

The use of infrared thermal imaging as a marker of tissue perfusion and predictor of arteriovenous fistula outcomes

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Abstract

Haemodialysis is a lifeline therapy for patients with end stage renal disease. An important factor in the survival of renal dialysis patients is the surgical creation of vascular access. The accepted gold standard of vascular access is the autologous arteriovenous fistula. Unfortunately it is associated with high rates of failing to mature. Therefore the ability to predict arteriovenous fistula outcomes following surgery would change current clinical practice.

Predictive markers of arteriovenous fistula outcomes are assessed in chapter 2 of the thesis. The different studies in the literature and our study have shown numerous contradictions and therefore no single factor was found to help accurately predict arteriovenous fistula maturation. In chapter 3 we assessed a multifactorial approach with a systematic review of the literature on predictive models of maturation. The review found a small number of predictive models in vascular access. The disparity between each study limits the development of a unified predictive model and none of the models are currently used in clinical practice.

Infrared thermal imaging has been available for decades but recent development in technology has made it small, portable and easy to use. In Chapter 4, we proved that this newly available hardware is a valid, accurate and user-friendly method of measuring skin temperature in humans and is comparable to more traditional methods of thermometry. Another principal finding from our thesis is that infrared thermal imaging can be used to quantify reactive hyperaemia following a vascular occlusion test in healthy volunteers and therefore is able to quantify haemodynamic changes in tissue perfusion (chapter 5).

Finally the IRTIVA study (Chapter 6) has shown that infrared thermal imaging is a very useful tool in accurately predicting fistula patency and maturation. For clinical patency, infrared thermal imaging was found to have a positive predictive value of 88% and a negative predictive value of 86%. For functional maturation, it was found to have a positive predictive value of 84%, a negative predictive value of 95%. In addition, it was shown to have superiority to the commonly used intra-operative predictor of thrill as well as other independent pre-operative patient factors.

From the thesis, it is clear that infrared thermal imaging has a definite role in renal patients with vascular access. In addition, there is great potential for its use in patients with other conditions such as peripheral vascular disease. It could be used as a non invasive near patient test in monitoring of outcomes following reperfusion interventions, both surgical and radiological ones. It might also be used as a predictor of outcome following renal transplantation. Therefore this thesis will be followed by research projects establishing the use of infrared thermal imaging in both peripheral vascular disease and renal transplantation.

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I thank my parents for inspiring me to pursue my dreams. I am eternally grateful to my wife Neba for her unconditional love, unending support and encouragement throughout this research.

This thesis is dedicated to both Neba and our wonderful son Adam

Declaration

The work presented in this thesis was undertaken during a dedicated period of research between 2014 and 2017 in the Department of Renal Surgery at the University Hospital Birmingham, UK.

I declare that the work presented in this thesis was undertaken by me except where indicated below:

Statistical analysis for chapter 6 was performed with the support and assistance of James Hodson (University Hospital Birmingham) especially for the ROC curve analysis and logistic regression model.

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List of publications arising from the work of this thesis

- 1 **Al Shakarchi J**, Hodson J, Field M, Inston N. Novel use of Infrared Thermal Imaging to predict arteriovenous fistula patency and maturation. *J Vasc Access*. 2017 18(4) :313-318 (**Chapter 6**)
- 2 **Al Shakarchi J**, Mellor S, Inston N. The novel use of infrared thermal imaging as an adjunct for the management of haemodialysis access induced distal ischaemia. *J Vasc Access*. 2016 17(4):70-72
- 3 **Al Shakarchi J**, McGrogan D, Van der Veer S, Sperrin M, Inston N. Predictive models for arteriovenous fistula maturation. *J Vasc Access*. 2016 17(3):229-232 (**Chapter 3**)
- 4 **Al Shakarchi J**, Khawaja A, Cassidy DB, Houston JG, Inston N. Efficacy of the ulnar-basilic arteriovenous fistula for haemodialysis: A systematic review. *Ann Vasc Surg*. 2016 32:1-4.
- 5 **Al Shakarchi J**, Nath J, McGrogan D, Khawaja A, Field M, Jones RG, Inston N. End-stage vascular access failure: can we define and can we classify? *Clin Kidney J*. 2015 8(5):590-593.
- 6 **Al Shakarchi J**, Stolba J, Houston JG, Inston N. Surgical techniques for haemodialysis access-induced distal ischaemia. *J Vasc Access*. 2016 17(1):40-46.
- 7 **Al Shakarchi J**, McGrogan D, Yates PJ, Inston N. Use of biosynthetic grafts (Omniflow II) for high infection risk haemodialysis vascular access. *J Vasc Access*. 2016 9;17(2):151-154.
- 8 **Al Shakarchi J**, Houston G, Inston N. Early cannulation grafts for haemodialysis: a systematic review. *J Vasc Access*. 2015 16(6):493-497

- 9 **Al Shakarchi J**, Jones R, Houston G, Inston N. A review on the hemodialysis reliable outflow (HeRO) graft. *Eur J Vasc Endovasc Surg*. 2015 50(1):108-113
- 10 **Al Shakarchi J**, Inston N. Timing of cannulation of arteriovenous grafts : are we too cautious ? *Clin Kidney J*. 2015 8(3):290-292.

List of Abbreviations

APD: Automated Peritoneal Dialysis

AUROC: Area Under ROC

AVF: Arterio-Venous Fistula

AVG: Arterio-Venous Graft

BB: Brachio-Basilic

BC: Brachio-Cephalic

BP: Blood pressure

C: Celcius

CAPD: Continuous Ambulatory Peritoneal Dialysis

CFD: Computational fluid dynamics

CKD: Chronic Kidney Disease

CRP: C reactive protein

DASS: Dialysis access steal syndrome

DRIL: distal revascularization with interval ligation

DVT: Deep vein thrombosis

EPTFE: Expanded Polytetrafluoroethylene

ESRD: End stage renal disease

ESRF: End stage renal failure

F: Fahrenheit

FMD: Flow mediated dilatation

GFR: Glomerular Filtration Rate

HAIDI: Haemodialysis access induced distal ischaemia

HD: Haemodialysis

INR: international normalized ratio

IR: Infrared

IRTI: Infrared thermal imaging

KDOQI: Kidney Disease Outcomes Quality Initiative

NIRS: near infrared spectroscopy

PAI: proximalisation of the arterial inflow

PD: Peritoneal Dialysis

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PTFE: Polytetrafluoroethylene

RC: Radio-Cephalic

RRT: Renal Replacement Therapy

RUDI: revision using distal flow

STO2: tissue oxygen saturation

TDC: Tunnelled Dialysis Catheter

TRIPOD: Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis

VOT: Vascular occlusion test

VIH: Venous Intimal Hyperplasia

Chapter 1

Introduction

1.1 END STAGE RENAL FAILURE

Chronic kidney disease (CKD) is an important long-term condition caused by damage to the kidneys. It is initially without any specific symptoms and is detected incidentally on a routine blood test. In the later stages of the disease, patients might develop a number of signs and symptoms including hypertension, hyperkalaemia, fluid overload and anaemia. The kidney disease outcomes quality initiative (KDOQI) working group defined chronic kidney disease in adults as (National Kidney Foundation, 2002):

- Kidney damage for ≥ 3 months, as defined by structural or functional abnormalities of the kidney, with or without decreased glomerular filtration rate (GFR), manifesting by either:
 - Pathological abnormalities
 - Markers of kidney damage, including abnormalities in the composition of blood, urine or imaging tests.
- Decreased GFR, with or without evidence of kidney damage.

There are multiple causes of CKD and the damage is usually irreversible (U.S. Renal Data System, 2005). The most common causes are listed in table 1.1. Some patients with the condition might require renal replacement therapy in the form of either dialysis or transplantation. It has recently been shown to affect an important proportion of the general population with a prevalence of 11% in USA and Europe (Coresh et al, 2003). The number of patients diagnosed with CKD is likely to increase over time as the general population is living longer. Also diabetes mellitus is becoming more prevalent and it is one of the main causes of kidney damage (U.S. Renal Data System, 2005).

Common causes of CKD
Diabetes
Hypertension
Glomerulonephritis
Idiopathic
Reflux Nephropathy
Polycystic Kidney Disease
Vasculitis

Table 1.1: Causes of chronic kidney disease

The stages of CKD are based on the measured or estimated glomerular filtration rate (GFR) a measure of kidney function (Table 1.2). There are five stages including stage 1 where kidney function is normal (U.S. Renal Data System, 2005). The stages of CKD are useful tool for physician and aid in describing patients renal failure and in planning management.

STAGE	GFR	Description
1	>90	Normal renal function
2	60-90	Mildly reduced renal function
3	30-60	Moderately reduced renal function
4	15-30	Severely reduced renal function
5	<15	End stage renal failure

Table 1.2: The KDOQI stages of chronic kidney disease

Once a patient has reached CKD stage 5, quality of life has generally become poor and life expectancy considerably shortened if the condition is untreated. Through the use of renal replacement therapy, survival and quality of life of ESRF patients can be markedly improved. In one study, participants with stage 5 renal failure managed without dialysis had a 1-year and 2-year survival of 68 and 47%, whilst those patients who chose to have dialysis had survivals of 84 and 76% respectively. (Murtagh et al, 2007)

1.2 RENAL REPLACEMENT THERAPY

Renal replacement therapy (RRT) is provided to patients in end stage renal failure. It has been shown to both prolong survival and improve quality of life for these patients (Allredge et al, 2004). RRT can take the form of haemodialysis (HD), peritoneal dialysis (PD) or renal transplantation. Over the last 15 years, the number of patients on renal replacement therapy has nearly doubled in the United Kingdom (Figure 1.1)

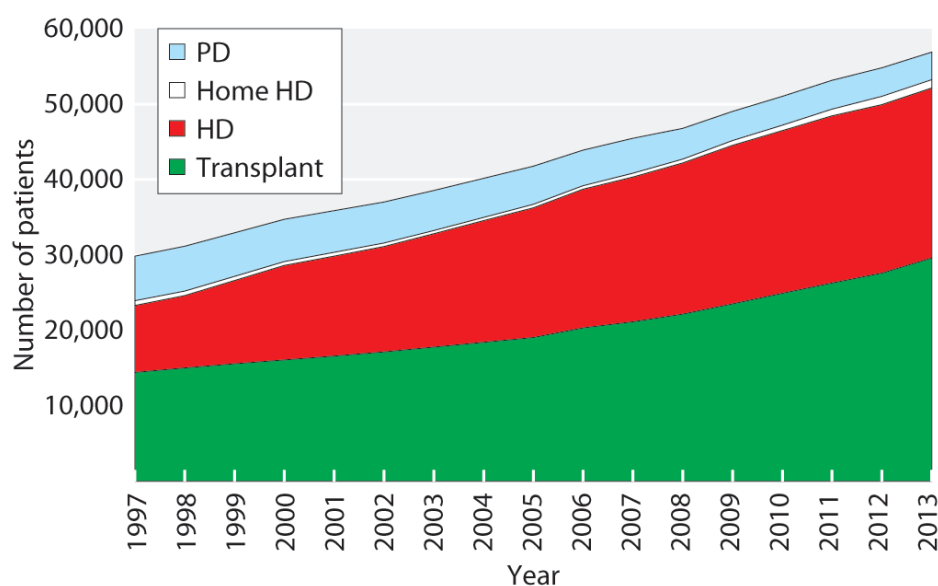


Figure 1.1: Growth in prevalent patients by treatment modality at the end of each year 1997–2013: UK renal registry data (Rao A., Casula A. and Castledine C., 2015)

The basic principle of haemodialysis is that it allows the diffusion of solutes across a semipermeable membrane by using a counter current flow. To achieve this, blood is diverted into a dialyser. In the machine, the dialysate fluid is flowing in the opposite direction to blood flow in the extracorporeal circuit. This counter-current flow maintains the concentration gradient across the membrane and increases the efficiency of the dialysis. Urea and other waste products such as potassium diffuse into the dialysis solution. However concentrations of sodium and other electrolytes

are similar to those of normal plasma to prevent any loss. Haemodialysis was first performed on an uraemic patient in 1924 at the university of Glessen in Germany (Haas, 1925). The radial and carotid arteries as well as the portal vein were cannulated for the procedure. Over the following 30 years, there were numerous improvements made to the dialysate fluid and machines used for HD. A significant and major advance in vascular access occurred in the 1960s when a nephrologist Cimino recalled his experience of traumatic arteriovenous fistulas in Korean war veterans and the ability for them to be needled regularly without any complications (Brescia et al, 1966). He worked closely with Brescia and Appell and the first arteriovenous fistula (AVF) was created. This new type of vascular access became very popular due to its longevity and safety. To this day AVFs are the most commonly used vascular access around the world and the gold standard.

Peritoneal dialysis involves the use of the peritoneum as a membrane across which fluids and substances are exchanged from plasma. A peritoneal catheter is placed surgically into the abdominal cavity to allow exchanges of dialysis fluid. There are two different types of peritoneal dialysis available: continuous ambulatory peritoneal dialysis (CAPD) and automated peritoneal dialysis (APD). As described by its name, CAPD is continuous and ambulatory. Dialysis fluid is inserted into the abdominal cavity and left there for four hours at a time to allow waste products to diffuse into it. This is repeated four times a day. APD involves the use of a machine and takes place at night for 8 to 10 hours. The dialysis solution is automatically delivered and drained from the abdominal cavity. Ganter was the first to use peritoneal lavage to treat renal failure in a patient with obstructive uropathy in 1923 (Ganter, 1923). The introduction of a safe and permanent catheter by Tenckhoff in 1968 in addition to the

novel concept of continuous dialysis in the 1970s resulted in the emergence of peritoneal dialysis as a viable renal replacement option (Tenckhoff and Curtis, 1970). Renal transplantation is another option for patients in end stage renal failure. Following transplantation experiments on animals in the early part of the 20th century, the first human kidney transplant was carried out by Voronoy in 1933 (Voronoy, 1933). Unfortunately the kidney was blood group incompatible and the patient died 48 hours after the transplant. As seen with this patient, the main obstacle to transplantation was immunological with high risk of rejection. This improved with the introduction of immunosuppressive therapies in the 1960s, which allowed for improved rate of successful renal transplantations and long-term results (Muntean and Lucan, 2013).

1.3 TYPES OF HAEMODIALYSIS VASCULAR ACCESS

Arterio-venous fistula (AVF)

An AVF is a surgically created connection between an artery and a vein, forming a high flow low resistance system allowing blood flow from the artery to the vein. As the vein adapts to the change in haemodynamics, the proximal vein becomes wider, more prominent and thick walled which facilitates repetitive cannulation for haemodialysis. This process called maturation can take up to 10 weeks to happen following AVF creation and therefore careful planning is required to ensure AVF formation is carried out prior to requiring haemodialysis (Wilmink et al, 2016). Nephrologist Cimino first described the concept of the AVF and its use as access for HD. Whilst working closely with fellow nephrologist Brescia and surgeon Appell, the first arteriovenous fistula was created 50 years ago (Brescia et al, 1966).

For practical purposes, AVF creation is normally conducted on the non-dominant arm to allow patients to be able to use their dominant hand during haemodialysis sessions. To preserve as many future access options as possible, guidelines recommend that the most distal AVF possible should be created in the first place (Navuluri and Regalado, 2009). Generally there are three forearm options available for the creation of an AVF: snuffbox, radio-cephalic and ulnar-basilic. The snuffbox fistula, created between the radial artery and the cephalic vein in the anatomical snuffbox of the hand is the most distal site and therefore gives a long segment of vein for needling. It preserves proximal vessels for creation of a further AV fistula in the case of failure, however the procedure is technically challenging and anatomically variable being feasible in only 50% of patients (Wolowczyk et al, 2000). The radio-cephalic fistula, formed between the radial artery and the cephalic vein at

the wrist is the most commonly created AVF and has shown to have good long-term outcomes. Whilst some authors have advocated the creation of ulnar-basilic fistulas, between the ulnar artery at the medial aspect of the wrist and the accompanying basilica vein, and despite its popularity in France, it has not gained recognition worldwide and remains a rarely performed AVF. The Gracz fistula is a proximal forearm arteriovenous fistula involving an end-to-side anastomosis between a perforating branch of the cephalic or median antecubital vein and the proximal radial artery.

If a forearm AVF is not a viable option, a brachiocephalic fistula, between the brachial artery and the cephalic vein in the antecubital fossa, is most commonly used. Brachiobasilic AVF formation is more challenging for the surgeon as it requires mobilisation and superficialisation of the basilic vein to make it more superficial for future needling. This can be done as a single procedure, joining the basilic vein to the brachial artery at the elbow and mobilizing the upper arm basilica vein or more commonly as a two-stage procedure whereby the basilic vein is anastomosed in first instance followed by superficialisation in the second stage following maturation of the vein.

Arterio-venous graft (AVG)

Arterio-venous grafts are used as an alternative when AVF formation is not feasible. They can be made of synthetic material such as polytetrafluoroethylene (PTFE) or biological material.

First described by Soyler in 1972, PTFE is a flexible and biocompatible material that may be repeatedly cannulated yet maintain its structural strength (Soyler et al, 1972). Interestingly a patent dispute for the graft took over 40 years to be settled. Peter

Cooper, a Gore employee, initiated and managed an experimental investigation on the suitability of expanded PTFE as a graft material. Goldfarb, a cardiologist at the Arizona Heart Institute, was among those who received the grafts from Gore for experimental testing and he altered the graft to make it suitable for human use. A dispute ensued and after over four decades, Goldfarb was finally awarded the patent.

The PTFE graft has become the most commonly used graft material. Whilst advances in synthetic grafts have occurred, most of these are adaptations on a basic expanded polytetrafluoroethylene (ePTFE) graft. Even though they do not require a maturation period, AVGs have traditionally not been cannulated within two weeks of placement but the current evidence does not support this established practice (Al Shakarchi and Inston, 2015). However new generation AVG have been reported as having self-sealing properties which allows early cannulation. They have been proven to allow safe early cannulation whilst having similar long-term patency results as standard ePTFE (Al Shakarchi, Houston and Inston, 2015).

Biological grafts have also been considered as haemodialysis conduits and these can be classified according to their origin. Those derived from patients themselves are called autografts, from human donors homografts (=allograft) and from non-human species xenografts. Autograft is when a vein is used in a heterotopic position, for example the saphenous vein has been used as a conduit in the arm. Homografts and xenografts have also been used but so far none have shown better results than ePTFE (Inston, 2015). However biological grafts may be useful in patients with high risk of infection (Al Shakarchi et al, 2016a).

Different anatomical variations can be used to form an arteriovenous graft. In the arm, the possible sites are in both the forearm and upper arm. These include a

straight radiocephalic, a loop brachiocephalic or a straight brachioaxillary AVG. Lower extremities can also be used for placing straight or loop grafts. Other unusual and rarely used placements are necklace grafts and grafts between lower and upper limbs such as a femoro-axillary AVG (Morsy, Khan and Chemla, 2008).

Tunnelled dialysis catheter (TDC)

Tunnelled dialysis catheters (TDC) are an option for vascular access, with the advantages of ease of insertion and immediate use. However they should only be used short term due to the high rate of both morbidity and mortality (Taylor et al, 2008). Shaldon was the first clinician to use catheters for haemodialysis and used a seldinger technique to insert them (Smith, 1967). Polyurethane and silicone are the two materials most commonly used in the manufacture of TDCs. These materials provide flexibility, durability and biocompatibility for intravascular use. Multiple designs are available but little evidence to support one over another is available. TDCs are used temporarily to provide vascular access whilst the patient awaits creation and maturation of an AVF or AVG. They can also be used when patients have run out of suitable options for permanent vascular access.

Until the 1990s, catheters were placed in subclavian veins but the site was found to cause a high rate of central vein stenosis. Thereafter insertion into the jugular vein has become standard practice although the femoral vein can also be used. In end stage vascular access, a final option is a translumbar catheter (Powell and Belfield, 2014).

Vascular Access type by country

Internationally, there is wide variation in the type of vascular access used. Japan has a high AVF use (>90%), whilst Canada's AVF use is below 50% (Figure 1.2). As demonstrated by DOPPS data, such variation in haemodialysis practice has undoubtedly an effect in long term patient outcomes and this is the reason why most countries have changed their policies and guidelines to increase the rate of AVF use. However survival outcome with access type is not consistent and variation in multiple factors must be considered when analyzing data. For example, conclusions made from Japanese HD patients are subject to substantially more uncertainty than that for U.S. patients due to both smaller sample size and lower event rate.

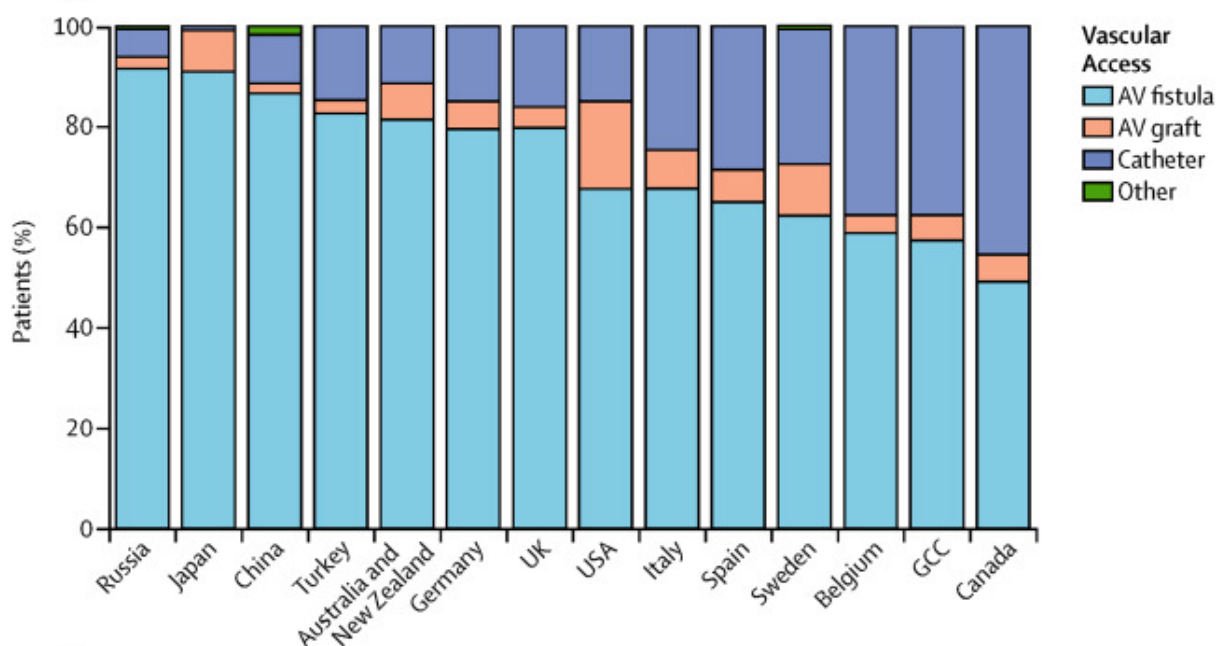


Figure 1.2: Type of Vascular Access used by country (Robinson BM et al, 2016)

1.4 COMPLICATIONS OF HAEMODIALYSIS VASCULAR ACCESS

Early failure/Late failure (non-maturation)

As previously mentioned, AVF is the first choice vascular access. However a significant number of fistulas (up to 50%) fail to adequately support haemodialysis following creation due to early failure or non-maturation (Dember et al, 2008). Early failure is defined by immediate failure of AVF within 72h of surgery due to thrombosis. The likely causes for this are surgical technique, poor arterial inflow or venous intimal fibrosis. An arteriovenous fistula needs to go through a maturation period before it can be used for dialysis. Maturation simply implies the fistula has dilated, become more prominent and thick walled which allows repetitive cannulation for haemodialysis.

Definitions of maturation are multiple. The rule of the 6s describes an easy method to assess AVF maturation at 6 weeks (National Kidney Foundation, 2006):

1. an adequate diameter (> 6 mm)
2. adequate access flow rate (~600 ml/min)
3. sufficiently superficial (<0.6 cm deep)

Other definitions include successful 2-needle cannulation of the AVF for dialysis.

Unfortunately late failure (non-maturation) is an important complication of AVF formation (Dember et al, 2008). Creation of an arteriovenous fistula involves the surgical anastomosis of a high-pressure artery to a low-pressure venous system. Most of the arterial blood flow diverts into the vein as a result of low resistance. Adequate perfusion of the tissue distal to the fistula requires sufficient dilatation of the proximal arterial system and increase in cardiac output to compensate for the diversion of blood flow through the fistula. Normal brachial arterial blood flow is 50

ml/min with radial blood flow rates of around 25 ml/min (Wedgwood, Wiggins and Guillou, 1984). A successful AVF will normally have a blood flow of at least 500ml/min, therefore the artery flow must increase at least 10-20 fold in order to deliver adequate blood flow and achieve AVF maturation. Therefore substantial arterial dilatation and remodeling is required for successful fistula maturation. However in most cases, the arterial flow does not increase sufficiently to allow maturation and therefore retrograde blood flow (also known as physiological steal) in the distal artery occurs. If the steal is severe, it can lead to tissue ischaemia (Dixon, 2006). However most patients are asymptomatic due to collateral arteries which reconstitute below the AVF therefore maintaining distal perfusion (Inston et al, 2017). The increased blood flow in the vein following AVF creation also causes an increase in wall shear stress (WSS), which leads to venous wall thickening and arterialization (Hammes, 2015). Normally the luminal diameter will increase in an attempt to reduce the WSS back to pre-AVF levels resulting in a dilated vein with a thickened wall, the perfect vessel to use for hemodialysis (Hammes, 2015). This flow-mediated dilatation occurs via endothelial-mediated responses such as the release of nitric oxide and other endothelium-dependent vasodilators (Corpataux et al, 2002).

Causes of non-maturation range from poor arterial inflow (inadequate vessel diameter, atherosclerotic disease, anastomosis of small size, chronic hypotension), post-anastomotic vein stenosis (possibly due to clamping damage), lack of ligation of tributary veins and venous fibrosis secondary to trauma from previous needling.

Vascular Access Stenosis

Vascular access stenosis can develop at any site along the AVF/AVG and can be described mostly anatomically with: anastomotic, post-anastomotic, puncture-related

or venous outflow. The diagnosis of vascular access stenosis can be accurately done in the majority of arteriovenous fistulas by physical examination alone. Imaging such as ultrasonography or fistulography can be used to confirm the clinical suspicion and define morphology.

The aetiology of VA stenoses is:

- Surgical - anastomotic stenosis
- Clamp damage - post-anastomotic
- Neointimal hyperplasia - post-anastomotic and venous outflow.
- Puncture technique - puncture related stenosis

Surgical anastomotic stenosis may occur where the anastomosis has been created too tightly although as the anastomosis is a fixed size it may be a relative stenosis as maturation occurs the adjacent vessel distends. In low flow situations this may be regarded as a stenosis but if high flow occurs within the AVF this simply represents a flow controlling area and should not be treated.

Neointimal hyperplasia has been the subject of extensive research to improve AVF/AVG patency rates (Roy-Chaudhury, 2007). Research has been focused on how to inhibit the two main pathological factors involved in the development of this complication: shear stress and endothelial cell proliferation. Shear stress has been proven to be the main cause of neointimal proliferation by experimental flow models (Lee and Roy-Chaudhury, 2009).

Management of stenotic lesions is either surgical or endovascular (balloon dilatation or stent placement). The KDOQI Guidelines recommend that stenoses should be treated with angioplasty or surgical revision if the stenosis is >50% of the lumen diameter and is associated with any clinical abnormality such as prolonged post-dialysis bleeding or difficulties in cannulation (National Kidney Foundation, 2006).

Central Vein Stenosis

Central vein stenosis is commonly associated with placement of central venous catheters and other devices (eg. pacemaker wires). Risk factors for stenosis development are a history of multiple catheters, long duration of catheter use, insertion in the subclavian vein and placement on the left-hand side of neck (Agarwal, Patel and Haddad, 2007). Endothelial injury with subsequent changes in the vessel wall results in development of micro-thrombi, smooth muscle proliferation, and central vein stenosis. Central vein stenosis can be asymptomatic and present with oedema of the ipsilateral upper limb following vascular access formation due to the increased flow (Agarwal, 2015). They are also a known factor for failure to mature following AVF formation. Endovascular interventions are the mainstay of management of central vein stenosis. Percutaneous angioplasty and stent placement can restore the functionality of the vascular access. Frequent or multiple interventions are usually required to keep the central vein patent (Maya, Saddekni and Allon, 2007). Studies on the mechanisms of development of central vein stenosis has led to the development of drug eluting balloon angioplasty which might improve outcome following intervention (Massmann et al, 2015). Prevention of central vein stenosis is the key to avoid access failure and other complications from central vein stenosis and relies upon avoidance of central vein stenosis placement and timely placement of arteriovenous fistula in prospective dialysis patient.

The HeRO graft is a new solution to this difficult problem (Al Shakarchi et al, 2015). It consists of two elements: an arteriovenous graft and a venous outflow component. The venous component is inserted percutaneously straight into the right atrium bypassing any central stenosis. The arteriovenous graft is anastomosed to the ipsilateral brachial artery and the two components are connected together using a

specially made titanium connector.

Vascular Access Infection

Infection is a serious complication of dialysis vascular access, which has an important impact on both access outcome and patient survival. Infection can develop at puncture sites due to poor aseptic technique or haematoma formation. Therefore infection prevention is critical for vascular access maintenance by strict adherence to aseptic and antiseptic protocols by the nursing staff (Grabe, Jakobsen and Damm, 1985).

AVF or AVG infection should always be managed as an emergency condition that requires hospitalisation since it can lead to rupture with bleeding or sepsis. Aggressive empirical antibiotic therapy should be started immediately on admission until culture results are available (Ryan, Calligaro and Dougherty, 2004). Removal of an infected AVG may be required as antibiotics have poor infiltration to foreign materials. This will usually involve inserting and using a temporary central dialysis catheter whilst creating a new vascular access at a different site.

ArterioVenous Access Ischaemic Steal (AVAIS)

Also referred to as dialysis associated steal syndrome (DASS) or haemodialysis access induced distal ischaemia (HAIDI), it occurs in up to 8% of patients (Beathard and Spergel, 2013). As previously explained, haemodynamic changes occur in the arm following AVF creation, which lead to physiological steal. If collateral vessels are poor or there is proximal arterial disease, clinical steal will occur and patients will be symptomatic. Clinical steal can be subdivided into early (<1month) or late (>1month) depending on the time of onset of symptoms. Early clinical steal is more often seen

in AVG whilst late clinical steal is usually seen in AVF. The reason for this is that AVF require a maturation process with venous diameter and flow rate increasing over time, whereas AVG have a set diameter which will lead to an immediate increase in flow rate.

Following the creation of upper limb vascular access, patients may develop a cold painful hand with neurological deficits or in extreme cases distal gangrene and ulceration. The incidence is higher in upper arm arteriovenous fistulas and grafts than in forearm vascular access due to the single arterial supply (Tordoir, Dammers and Van Der Sande, 2004). Risk factors for AVAIS are diabetes and peripheral vascular disease. Clinically AVAIS is similar to that of peripheral vascular disease and can be classified according to symptoms (Tordoir, Dammers and Van Der Sande, 2004).

Stage I	Cold/Pale hand without pain
Stage II	Pain on exertion and/or during haemodialysis
Stage III	Pain at rest
Stage IV	Ulceration/necrosis/gangrene

The diagnosis of steal syndrome is made clinically and can be confirmed by color Doppler ultrasound and other complementary imaging. Management of this complication traditionally was ligation of the vascular access. To preserve the vascular access, a number of different surgical procedures have been proposed which include banding, revision using distal inflow (RUDI), proximalisation of access inflow (PAI) and distal revascularization interval ligation (DRIL) (Al Shakarchi et al, 2016b).

Pseudoaneurysms/Aneurysms

Pseudoaneurysms are puncture-related complications of both AVF and AVG. The trigger event is a traumatic cannulation during haemodialysis or an anastomotic leak following surgery with subsequent haematoma formation around the vessel (Valenti, Mistry and Stephenson, 2014). The size of the haematoma may vary widely and inadequate compression at puncture site favours further haematoma growth. Once the haematoma is formed around the fistula vein or graft, it develops a fibrotic sac but this is not lined by any endothelium. Ultrasound guided direct thrombin injection into the pseudoaneurysm sac has been used however surgical revision has been the standard approach to manage pseudoaneurysms (Keeling et al, 2008). Endovascular treatment using covered stents insertion has also been advocated to treat such complications. This method has proven to be both safe and effective and the results have been encouraging so far (Ananthakrishnan et al, 2008).

True aneurysms are widened or enlarged segments of the arterialized vein that may develop at puncture site or at the anastomosis. Aneurysms may reach significant sizes. If they present with a rapid increase in size, pain, thinning of the overlying skin or infection, they should be managed emergently with ligation as they are at high risk of rupture (Uysal and Ceviker, 2016). In other circumstances where the aneurysm is slow growing, they can be managed conservatively with aesthetic reasons being the main indication for surgery. Obviously in this setting, the desired outcome should be preservation of definitive access where possible and excision of the aneurysm with plication is a suitable surgical option.

Heart failure

It is an uncommon complication and occurs in high flow fistulas (Bourquelot, 2016). It

is generally defined as an AVF with flows over 1l/minute at the forearm and over 1.5l/minute at the upper arm (Sequeira and Tan, 2015). It has also been described as access with a flow that is >20% of cardiac output (Pandeya and Lindsay, 1999). Although a large number of patients might not develop any symptoms, high flow access may lead to high output cardiac failure or pulmonary hypertension. Anaemia and underlying heart disease are also important pre-disposing risk factors. Surgical banding may relieve symptoms but in cases of persistent symptoms, ligation of the vascular access is the only remaining option.

1.5 PREDICTORS OF ARTERIOVENOUS FISTULA MATURATION

Clinical and ultrasound assessment

Clinical assessment has been used to choose the location of arterio-venous fistula formation. Assessment of venous size and arterial pulse by palpation was traditionally carried out pre-operatively in clinic prior to listing. Duplex ultrasonography has been used as an adjunct to clinical examination to assess more accurately the size of both artery and vein. It has been shown that a larger venous diameter improves maturation rate. Studies carried out previously have suggested that preoperative ultrasound mapping of venous diameters versus no mapping is beneficial, but did not reach statistical significance (Nakata et al, 2016). Utilization of different cut off values can have significant effects on maturation rates. Therefore ultrasound scanning pre-operatively should be carried out on all patients and measurement taken to ensure that the chosen vein is of suitable diameter (Ferring, Henderson and Wilmink, 2014). There is also evidence that artery size has an effect on maturation rate and should be assessed too. Fistula site has been shown to be a predictor of maturation with brachiocephalic being more likely to mature than radiocephalic arterio-venous fistulas. However this might well be related to venous and arterial sizes being generally larger at the elbow than at the wrist.

Demographics

The hemodialysis fistula maturation study looked extensively at pre-operative factors that could predict early fistula thrombosis (Farber et al, 2016). This multicentre study included a large cohort of patients and looked specifically at the following demographic and clinical factors: gender, age, ethnicity, work status, body mass

index, smoking status, hypercoagulability disorder, co-morbidities, cause of renal failure and current maintenance haemodialysis. Interestingly despite looking so extensively, the only significant factor found as a predictor of early thrombosis was female gender (Farber et al, 2016). Of note, diabetes was found to be inversely associated with early thrombosis, even when adjusted for potential cofounders.

Blood biomarkers

Blood biomarkers have been found to be predictive in numerous medical conditions. The use of biomarkers in the diagnosis and management of cardiovascular disease, infections and cancer are well established in current practice (Mayeux et al, 2004). As yet there has been no single blood biomarkers identified as a useful predictor to AVF maturation. While routine ultrasound screening may improve AVF survival rates by allowing early identification of fistulas at risk of failure, this is time and labour intensive. In contrast, the detection of blood biomarkers might allow a more cost effective way to identify patients at higher risk of AVF failure. Few studies have assessed the relationship between blood biomarkers (eg. soluble e-selectin) and AVF failure and there is discrepancy between the conclusions reported (Kirkpantur et al, 2008; Bilgic et al, 2015). A lot of these studies also focused on a small number of biomarkers (eg. Osteoprotegerin, red blood cell distribution) and included a relatively small number of patients (Bojakowski et al, 2012; Kim, Kim and Oh, 2013).

1.6 BASICS OF INFRARED THERMAL IMAGING

The electromagnetic spectrum contains an array of electromagnetic waves with a range of frequency and wavelength. Visible light is a small part of that radiation distribution but the only one that the human eye can discriminate. On the higher frequency side of the electromagnetic spectrum, we can find the ultraviolet waves, the x-rays and the Gamma rays whilst on the lower frequencies we find the infrared, microwaves and radio waves (National Aeronautics and Space Administration, 2016).

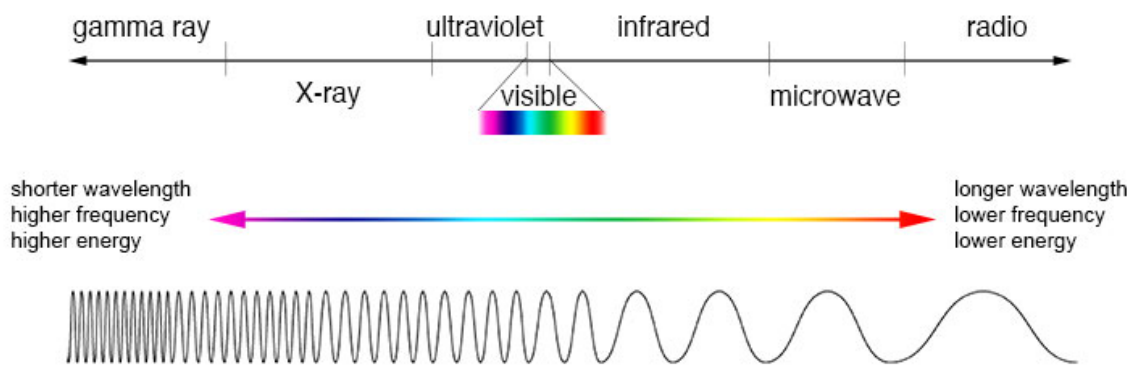


Figure 1.3: The electromagnetic spectrum (National Aeronautics and Space Administration, 2016)

All objects above the temperature of absolute zero (-273.15°C) radiate and absorb energy in the form of electromagnetic radiation and the quantity of electromagnetic energy radiated is related to its temperature, surface area and the type of surface (Thomas, 1999). A perfect black body does not reflect radiation from its surface and absorbs 100% of the incident radiation. This makes it a perfect absorber and inversely it is also a perfect radiator/emitter of radiant energy. The radiative property of an object is expressed as emissivity, which is calculated as the ratio of energy emitted by an object over the energy emitted by a black body at the same

temperature (Thomas, 1999). Therefore emissivity value can range between 0 and 1, with a perfect black body having a value equal to 1. Human skin has been found to be an almost perfect radiator with emissivity values ranging between 0.96 and 0.98 (Houdas and Ring, 1982). Therefore thermal radiation emitted from skin is very closely related to the actual skin temperature and in turn infrared thermography is well suited for skin temperature measurement. It has also been shown that there is no difference in skin emissivity based on skin colour and therefore measurements from thermograms are independent of ethnicity (Jones, 1998). It is important to also note that emissivity depends on the viewing angle as it remains constant until $\sim 50^\circ$ however at greater angles, the emissivity does decrease (Dozier and Warren, 1982). Unlike a perfect black body, this is due to the fact that normal surfaces do not emit infrared radiation similarly in all directions.

In 1800, astronomer William Herschel was the first to discover infrared radiation whilst experimenting on sunlight passing through a glass prism (Scott Barr, 1961). He found that IR could be reflected like visible light and detected by thermometry. The first ever thermogram was actually recorded by his son John Herschel in 1840. In the middle of the 20th century, an increase interest in the subject led to the first electronic sensors for the detection of IR radiation being developed (Dereniak and Boreman, 1996). The military industry took a vivid interest in the technology and adapted it to be used for night vision. Infrared thermal imaging continued during most of the 20th century to be used primarily for military and space applications. This led to the technology being improved rapidly over time. Initially acquiring a thermal image would be both time consuming and technically challenging with the image quality and resolution being generally poor. However through the development of bolometer cameras, the technology has now become much more advanced and user friendly

(Dereniak and Boreman, 1996). Infrared radiation strikes the detector (microbolometer), which is made of a grid of sensors over a grid of silicon, and changes its electrical resistance. This change is then processed into temperatures, which can then be used to create an image. The microbolometer is an uncooled thermal sensor, thus avoids the requirement of bulky expensive cooling techniques. Therefore these cameras have cost, size, power and reliability advantages over their predecessors (Wang et al, 2005). These cameras originally developed in the 1970s were initially restricted to military uses only until the end of the 20th century. Technical advances in both software and hardware have improved dramatically over last decade. Today's infrared thermal imaging (IRTI) cameras are reliable, accurate, cost effective and considerably more portable than previously. This has happened by industrial and military use of the technology rather than scientific use. However medicine might well benefit from this as IRTI has many potential clinical uses. Even though it has had previous interest from clinicians and scientists, there has been a resurgence of clinical applications of its use, seen by a number of recently published papers (Ring and Ammer, 2012).

Thermal images are actually visual displays of the amount of infrared energy emitted, transmitted, and reflected by an object. A thermal imaging camera is capable of performing algorithms to interpret that data, build an image and calculate the temperature. It is also important to understand the different terminologies used in this topic and the commission of the European Association of Thermology defined these (Terminology Commission of European Association of Thermology, 1978):

- Thermology: General term for the study of the nature and effects of heat and thermal energy.
- Thermometry: Measure of one parameter of the thermal state of a body,

which is temperature.

- Thermography: Recording of the temperature or temperature distribution of a body (whether obtained by conduction, convection or radiation).

1.7 INFRARED THERMAL IMAGING IN MEDICINE

One of the simplest measurements taken by any clinician is a patient's temperature as it is a long established indicator of health. Humans are able to maintain a constant temperature, as part of homeostasis to allow normal tissue function (Guyton and Hall, 2006). Change in the core temperature is a clear sign of bodily dysfunction. Body temperature has traditionally been measured using a thermometer, however IRTI has also been used, mainly for research purposes for over 50 years. It has been used to study numerous medical conditions where skin temperature can reflect the presence of inflammation in the underlying tissues, or where blood flow has changed due to a clinical abnormality. IRTI can be applied in medicine either as a screening tool or diagnostic test.

Peripheral circulation

In some vascular conditions, such as Raynaud's disease, the effect of local blood circulation on skin temperature has been assessed by IRTI (Ammer, 2009). This was carried out after exposure of the hands to a temperature stimulus. In normal healthy subjects this leads to a reactive hyperaemia of the fingers, while in Raynaud's sufferers there is a slow protracted recovery to baseline. This test has been applied, to allow quantification in many different studies and trials of vasodilator treatments (Ammer, 2009).

A study from China has looked at the use of thermography in the diagnosis of suspected cases of deep vein thrombosis. Assessing this first in an animal model and confirming their initial findings in humans with a diagnostic concordance rate of 96.9% (Deng et al, 2012; Deng et al 2015). They concluded that IRTI could serve as a novel effective detection and screening tool for DVT.

There have also been reports of the use of IRTI in the field of vascular access. Allen et al investigated the use of thermography in patients with suspected steal syndrome from dialysis access arteriovenous fistulas and found an agreement between its use and clinical assessment of steal syndrome (Allen et al, 2006). Similarly Novljan et al found similar results and therefore concluded that whilst the diagnosis of steal syndrome is primarily clinical, thermography might be a safe, non-invasive, cheap tool for the timely detection of at risk patients (Novljan et al, 2011). In addition thermography may allow quantitative monitoring which may precede clinical improvement.

Malignant diseases

Melanoma identification was one of the first clinical applications of infrared thermal imaging (Di Carlo, 1995). The value of IRTI for diagnosis of malignant melanomas has been a subject of controversy in the past (Maillard and Hessler, 1969; Cristofolini et al, 1981). However recent studies have shown that malignant and benign melanomas have different patterns of temperature changes (Cristofolini et al, 1981). The use of IRTI has been investigated in the detection of breast carcinoma. Arora et al investigated the use of thermography in 92 patients whom a breast biopsy had been recommended based on prior mammogram or ultrasound (Arora et al, 2008). They demonstrated that IRTI identified 58 of the 60 malignancies with a sensitivity of 97% and a specificity of 44% and concluded that infrared thermal imaging was a valuable adjunct to mammography and ultrasound. Further studies in breast cancer (Rassiwala et al) assessed the use of IRTI as a screening tool in a study including 1008 patients (Rassiwala et al, 2014). Based on these results, thermography was evaluated as a very useful tool for screening breast carcinoma as it is non-contact,

pain-free, radiation free and comparatively inexpensive.

Intraoperative IRTI has been studied in neurosurgery as a novel technique to locate the margins of primary and metastatic brain tumors. Kateb et al have suggested that thermal imaging could be used to provide a rapid, non-invasive, and real-time intra-operative imaging adjunct (Kateb et al, 2009).

Inflammatory arthritis

Rheumatoid arthritis was one of the earliest conditions where thermography was used clinically. Ring et al showed that the surface temperature of an arthritic joint closely reflected the intra-articular joint, and to other biochemical markers of inflammation obtained from the exudate (Ring and Collins, 1970). Collins et al showed that IRTI can be used for the assessment of joint involvement in inflammatory arthritis (Collins et al, 1974). Recently, a pilot study from the United States found a strong correlation between high temperature and swelling of finger joints detected by three-dimensional images. The authors developed a heat distribution index using IRTI, which had a diagnostic sensitivity of 67% and a specificity of 100% for arthritic swelling (Spalding et al, 2008).

Soft tissue injury

Muscle action is one of the most important sources of increased metabolic heat. Acute muscle injuries may be recognized by areas of increased temperature due to inflammation in the early state of trauma (Schmitt and Guillot, 1984). However, long lasting injuries and also scar tissue can appear as hypothermic areas due to reduced muscle contraction, and therefore reduced heat production. Similar areas of reduced temperature have been found adjacent to peripheral joints with a decreased range of

movement due to inflammation or pain (Ammer, 1995). Silva et al assessed the use of IRTI in paediatric patients and found that although suboptimal, performance in finding the site of injury was encouraging and should be further evaluated (Silva et al, 2012). Yang et al proved that IRTI can show temperature changes in ligamentous injury and can be applied in the evaluation of medial collateral ligament injuries (Yang et al, 2014).

Burns & Plastic Surgery

Reports by Cole et al in the 1990s showed promise for the use of IRTI in the assessment of burns (Cole, Jones and Shakespeare, 1990; Cole et al, 1991) and more recently a British group aimed to investigate the use of thermography in the assessment of burn depth (Hardwicke et al, 2013). Eleven patients with burns affecting different parts of the body were included in this study that found that thermal imaging could determine differences in burn depth.

In reconstructive surgery, De Weerd et al have shown that the design of deep inferior epigastric artery perforator flaps, which are used for breast reconstruction, can be based on dynamic infrared thermal imaging for pre-surgical selection of the vessel (De Weerd, Mercer and Setsa, 2006). The same group of researchers also showed IRTI to be a valuable tool for both intra-operative and post-operative monitoring in flap surgery (De Weerd, Weum and Mercer, 2009; De Weerd, Miland and Mercer, 2009). Thermography has recently been shown to be a quick, easy method of assessing cutaneous perforators. It should be considered a useful adjunct, and further investigated, to determine its best role among the established perforator imaging methods (Sheena et al, 2013).

Diabetes

Sivanandam et al investigated the potential of IRTI in diagnosing as well as predicting type 2 diabetes compared with biochemical assay of HbA1c as standard (Sivanandam et al, 2012). They found that diabetic patients had lower cutaneous temperature at various anatomical sites compared to healthy individuals. Palmar temperature could be used for diabetes diagnosis (threshold <33.85 degrees) with sensitivity of 90% and specificity of 56%. They also found that as HbA1c increases, skin temperature decreases. They then concluded that thermography could be used as a diagnostic as well as prognostic tool for diabetes.

Van Netten et al also explored the use of IRTI in diabetes, in particular in detecting diabetic foot problems and found that areas with complications had a significant lower temperature than the rest of the foot or when compared to the contralateral side (Van Netten et al, 2013).

Renal Transplantation

There have been reports of the use of infrared thermal imaging during renal transplantation. Gorbach et al investigated the use of IRTI in 13 transplanted patients and found that renal rewarming time as determined by thermography correlated with cold ischaemic time (Gorbach et al, 2003). They also found that it could predict return of renal function.

Surgical site infection

A Japanese plastic surgery group presented a case report of the use of IRTI in screening for post operative infection following the Nuss procedure (minimally invasive procedure to treat pectus excavatum) and found that Infrared thermography

camera clearly indicated slight cellulitis in the right chest (Fujita et al, 2013).

Evidence of diagnostic use of IRTI in cancers, peripheral vascular and musculoskeletal conditions demonstrates value in pursuing further studies in this technology.

The data to date is from single centre studies involving a small number of subjects and as such do not represent a driver for clinical change and is important to not overstate the clinical uses of thermography until more robust studies are performed.

Despite this the technology is available, cheap, non invasive and can be used with minimal training in all areas of healthcare delivery. The results are produced in real time and can be transmitted easily by electronic means.

In conclusion there is great potential in the use of infrared thermal imaging in medicine as a non-invasive near patient test and further studies of its use are awaited.

Chapter 2

Predictive markers of arteriovenous fistula functional maturation

2.1 ABSTRACT

Native Arteriovenous fistulas are the gold standard for haemodialysis vascular access. Unfortunately they have a high rate of failure to mature. In this study we aim to assess different pre-operative blood and anatomical markers in predicting fistula maturation.

Our prospectively collected cohort study included consecutive patients who underwent fistula formation for dialysis. Pre-operative markers assessed included systolic & diastolic blood pressure as well as numerous haematological and biochemical blood tests. Arterial and venous diameters were also included as anatomical markers.

110 patients were included with a median age of 60 (range: 18-84). Our results showed that increased venous diameter was found to correlate significantly with improved outcome. A low haemoglobin and white cell count were also found to be significant positive predictive parameters.

In conclusion our study has shown venous diameter to be a significant predictor of maturation. However the literature and our study have shown numerous contradictions regarding blood markers and therefore no single factor can help accurately predict arteriovenous fistula maturation. A multifactorial approach may be required in the form of predictive modelling, assessing a combination of blood markers, anatomical factors and demographics.

2.2 INTRODUCTION

Haemodialysis (HD) is a lifeline therapy for patients with end stage renal disease (ESRD). It is estimated that over 1.5 million patients receive regular HD treatment worldwide (Grassmann et al, 2005). An important factor in the survival of renal dialysis patients is the surgical creation of vascular access. The accepted gold standard of vascular access is the autologous arteriovenous fistula (AVF). Three important steps are required for a fistula to successfully mature and be used for dialysis: venous dilatation, sufficient blood flow and the fistula must be superficial enough to allow needling. Unfortunately AVFs are known to be associated with non-maturation and poor long-term patency (Nikam et al, 2012; Al-Jaishi et al, 2014). Early identification of fistulas at risk of non-maturation can help guide salvage intervention (Al-Jaishi et al, 2014). Numerous factors such as venous diameter have been suggested as having an effect on the success rate of maturation (Smith, Gohil and Chetter, 2012).

In this study we aim to assess the prognostic role of blood tests as well as anatomical markers for fistula maturation. This could allow us to monitor patients at a higher risk of failure as well as potentially finding novel therapeutic options.

2.3 METHOD

Prospective data was collected for consecutive patients with end stage renal disease referred at our tertiary specialist unit for single incision AVF formation under local anaesthetic between April and September 2009. All patients received pre-operative ultrasound mapping to select the most appropriate anatomical site dictated by vessel diameters in a specialist clinic to attempt to minimize environmental factors such as room temperature. Demographic and physiological data were also gathered, namely - sex, age and co-morbidities, grade of operating surgeon, type of AVF created (radio-cephalic, brachio-cephalic and brachio-basilic) and ultrasound results. The pre-operative blood biomarkers assessed were haemoglobin, white cell count, platelets, INR, CRP, cholesterol, triglyceride, urea, creatinine, phosphate, magnesium and folate level. Venous and arterial diameters as anatomical geometrics as well as systolic and diastolic blood pressure were also assessed as predictive markers. This cohort was followed up over 4 years until August 2013. Maturation was defined as ability to use the AVF for adequate dialysis on at least two separate occasions. The study was approved by local audit review board (CARMS-11315) where specific patient consent was not deemed necessary as it was non-interventional and observational.

Statistical analysis

Collation of database and statistical analysis were carried out in SPSS release 2009 Version 18.0, PASW Statistics for Windows SPSS Inc, Chicago. Statistical analysis of pre-operative markers and outcomes was undertaken using unpaired student t-test where samples were normally distributed and Mann-Whitney U for non-normally

distributed data. Data are presented as mean and standard deviation (SD) (when data normally distributed) or median and inter-quartile range (IQR) (non-normally distributed). A p-value of 0.05 or less was considered statistically significant.

2.4 RESULTS

A total number of 110 patients underwent AVF formation and were included in the analysis. Their median age was 60 (range 18-84) with a female to male ratio of 2:1. Demographics of our cohort is described in table 2.1. The primary aetiology for the patients ESRD varied amongst the group. Diabetes and hypertensive nephropathy were the most common cause. The median follow up of patients was 50 months (range 3-53). 62% of our cohort successfully used their fistula for dialysis. We did not find any significant difference in outcomes depending on grade of surgeon.

Demographic	Population n (%)
Median Age	60y
Cause of ESRF	
Diabetes	21 (19%)
Unknown	16 (15%)
Hypertension	14 (13%)
Polycystic	7 (6%)
Vasculitis	6 (5%)
Operating surgeon	
Senior	34 (31%)
Middle Grade	46 (42%)
Junior	30 (27%)
Anaesthesia	
Local	101 (92%)
General	9 (8%)
Diabetes	33 (30%)
Hypertension	78 (71%)
Peripheral vascular disease	4 (4%)
Previous transplant	10 (9%)

Table 2.1: Demographics of patient cohort for predictive markers

The summary of our findings are described in Table 2.2. A larger venous diameter was associated with a significant increase in maturation of fistulas as well as a lower haemoglobin and white cell count. There were trends suggesting that a lower level of folate and magnesium were associated with better results. However, none of these were found to be significant and therefore it is difficult to make any conclusions from the results.

Factor	Functional maturation	N	Mean	Standard Deviation	P-value
Age	Yes	68	60.7	16.5	0.58
	No	42	58.9	17.6	
Vein Diameter	Yes	64	3.64	0.90	0.02
	No	39	3.18	0.94	
Artery Diameter	Yes	47	3.59	1.42	0.62
	No	33	3.43	1.37	
Systolic BP	Yes	39	149.2	31.8	0.9
	No	27	150.1	26.4	
Diastolic BP	Yes	39	79.5	13.4	0.82
	No	27	80.2	11.3	
Haemoglobin	Yes	68	11.23	1.97	0.04
	No	42	12.07	2.29	
White cell count	Yes	68	7.16	2.63	0.05
	No	42	8.2	2.68	
Platelets	Yes	68	228.7	74.6	0.74
	No	42	224.1	62.0	
INR	Yes	64	1.10	0.25	0.01
	No	39	0.99	0.09	
Cholesterol	Yes	65	4.44	1.43	0.88
	No	39	4.47	1.32	
Triglyceride	Yes	63	1.94	1.15	0.74
	No	36	1.85	1.24	
Urea	Yes	68	17.62	8.80	0.95
	No	42	17.73	9.65	
Creatinine	Yes	68	495.93	238.01	0.20
	No	42	442.05	171.89	
Phosphate	Yes	46	1.54	0.44	0.83
	No	32	1.56	0.40	
Magnesium	Yes	35	0.94	0.13	0.06
	No	25	1.01	0.14	
Folate	Yes	48	7.68	4.92	0.23
	No	32	9.12	5.74	
CRP	Yes	61	16.1	32.4	0.54
	No	34	20.3	30.3	

Table 2.2: Summary of the predictive accuracy of anatomical and blood markers

2.5 DISCUSSION

AVF maturation has been a difficult problem to deal with for clinicians worldwide. Many factors can have an effect in the success or failure of an AVF. We found a significant difference in outcome depending on the venous diameter. A larger intraluminal diameter of a vein was associated with a higher functional maturation rate. Studies carried out previously have suggested that preoperative ultrasound mapping of venous diameters versus no mapping is beneficial, but did not reach statistical significance (Wong et al, 2013). Utilization of different cut off values can have significant effects on maturation rates. Ultrasound scanning pre-operatively should be carried out on all patients and measurement taken to ensure that the chosen vein is of suitable diameter (Wong et al, 2013).

We did not find any significance to folate level. This is an interesting finding as Righetti et al had suggested that folic acid supplement was associated with an improvement in results of primary patency rate in fistula in a small cohort of patients (Righetti et al, 2009). However folic acid supplementation whilst on HD has been investigated in relation to cardiovascular events in patients with ESRD and does not appear to have any effect on venous access thrombosis (Wrone et al, 2004).

In our study, patients with a lower haemoglobin had better maturation rates which confirms the finding from a recently published study (Bashar et al, 2015). The low haemoglobin has been hypothesized to lead to upregulation of endothelial nitric oxide synthase leading to vasodilation, however this is yet to be confirmed by further studies (Bashar et al, 2015). However this is contradictory to previous evidence, which showed that haemoglobin level did not have an effect on outcome (Khavanin Zadeh, Gholipour and Hadipour, 2008). The better outcome associated with a lower

white cell count in our study contradicts other evidence in the literature (Bashar et al, 2015).

There was no difference in cholesterol level between the two patient groups (maturing vs non maturing). This explains the recent study from Birch et al which found that statin therapy did not decrease the number of stenotic lesions developing in AV fistulas. (Birch, Fillaus and Florescu, 2013).

Limitations of the study were the missing data from medical records as there was no pre-operative protocol for the blood tests. It is important to mention that unlike previous studies, we assessed functional maturation as defined by the ability to use the AVF for adequate dialysis on at least two separate occasions. It might mean that some patients whose renal function was stable and did not require haemodialysis were deemed as non-mature.

In conclusion the literature and our study have shown numerous contradictions and therefore no single factor was found to help accurately predict arteriovenous fistula maturation apart from venous diameter. Hence, predictive markers have not made it into routine clinical practice, however a minimum venous diameter of 2mm has been advocated (Smith, Gohil and Chetter, 2012). A multifactorial approach may be required in the form of predictive modelling, assessing a combination of blood markers, anatomical factors and demographics.

Chapter 3

Predictive Models of Arteriovenous Fistula Outcomes

3.1 ABSTRACT

Haemodialysis is a lifeline therapy for patients with end stage renal disease. A critical factor in the survival of renal dialysis patients is the surgical creation of vascular access and international guidelines recommend arteriovenous fistulas as the gold standard of vascular access for haemodialysis. Despite this, AVFs have been associated with high failure rates. Although risk factors for AVF failure have been identified, their utility for predicting AVF failure through predictive models remains unclear. The objectives of this review are to systematically and critically assess the methodology and reporting of studies developing prognostic predictive models for AVF outcomes and assess them for suitability in clinical practice.

Electronic databases were searched for studies reporting prognostic predictive models for AVF outcomes. Dual review was conducted to identify studies that reported on the development or validation of a model constructed to predict AVF outcome following creation. Data was extracted on study characteristics, risk predictors, statistical methodology, type of model as well as validation process. We included 4 different studies reporting five different predictive models. Parameters identified that were common to all scoring system were age and cardiovascular disease.

This review has found a small number of predictive models in vascular access. The disparity between each study limits the development of a unified predictive model.

3.2 INTRODUCTION

Predictive analytics has allowed for the development of accurate, patient-specific, predictive models that can aid in clinical decision-making. Predictive models can either be diagnostic or prognostic and are tools that combine multiple predictors to obtain a risk or probability. They are becoming increasingly described in the medical literature and used in clinical practice. These models have considerable potential to contribute to the decision-making process regarding the management of a patient. Typically, they combine several clinical, investigational or patient related measures to calculate the likelihood of an outcome.

Haemodialysis (HD) is a life preserving therapy for patients with end stage renal disease (ESRD). It is estimated that over 1.5 million patients receive regular HD treatment worldwide with the number growing at a rate of around 7% per year (Grassmann et al, 2005). A critical factor in the survival of renal dialysis patients is the surgical creation of vascular access and international guidelines recommend arteriovenous fistulas (AVF) as the gold standard of vascular access for HD (Vascular Access 2006 Work Group, 2006; Tordoir et al, 2007). Unfortunately, AVFs have been associated with high failure rates, being reported at 30 to 50% predominately due to aggressive pathological process termed venous intimal hyperplasia (VIH) (Nikam et al, 2012; Al-Jaishi et al, 2014). Numerous factors have been described as having an effect on the success rate and therefore a prognostic predictive model would be extremely important in planning in clinical practice for example guiding decisions on the site of the AVF (Smith, Gohil and Chetter, 2012). Existing reviews of prediction models in other diseases have shown that model design is critical and many models are poorly developed with weaknesses in their

methodology, validation and reporting (Collins et al, 2013).

The objectives of our review are to systematically and critically assess the methodology and reporting of studies developing prognostic predictive models for AVF outcomes and assess them for suitability in clinical practice.

3.3 METHOD

Searches of Pubmed central, Ovid Medline and Ovid Embase were performed using the combination of the following search terms: haemodialysis, haemofiltration or renal failure with vascular access, arteriovenous fistula or arteriovenous shunt in addition to the Haynes tool for finding prognostic prediction models to identify suitable published articles. In addition, the references cited in selected articles were reviewed for any further relevant available studies as well as our personal reference list. Articles were not restricted to any language and searches were carried out up to 31st May 2015. Grey literature was not searched or included. The systematic review was performed in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (Moher et al, 2009).

Articles were included if they aimed to develop a multivariable prognostic predictive model for AVF maturation or patency outcomes. Articles were excluded if they did not develop a new model or the outcome was different from the inclusion criteria.

Two reviewers (J.A. and D.M.) independently identified articles and screened them for inclusion. Disagreements were solved by consensus between authors. Where this was not possible, a 3rd opinion (N.I) was sought. Eligible articles were used to develop a potential prognostic assessment tool for predicting patency of arteriovenous fistula at 1-year. Studies that assess causal effect of a predictor(s) without modelling were excluded.

From each study, we extracted data on study design, population, outcome definition, setting, demographics, the number of patients included, the number of variables tested as predictors, model development and evaluation, the type of statistical model, using a data extraction sheet. Each study underwent assessment using the

TRIPOD (Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis) statement (Collins et al, 2015).

3.4 RESULTS

A total of 1378 articles and abstracts were identified using our search strategy. After screening the contents of the abstract, 16 full text articles underwent assessment for eligibility and quality inspection of methodology. (Figure 3.1) Following the assessment, 4 articles were found to be eligible for the review. (Table 3.1) One paper proposed two different models and therefore a total of five models have been included in our study. Three models were developed using North American data from Canada (Lok et al, 2006) and United States (Feldman et al, 2003) and the other two models were European from the United Kingdom (12,13). Of note, the two British papers only focused on one type of AVF each (radiocephalic & snuff box) (Twine et al, 2012; Bosanquet et al, 2015).

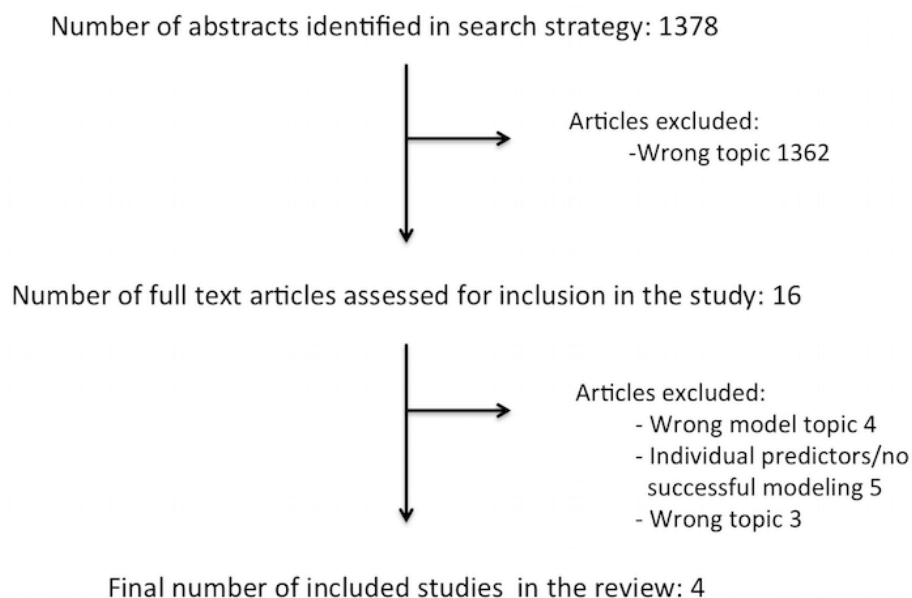


Figure 3.1: Flowsheet describing the results of the search strategy with inclusion and exclusions following screening stages

TRIPOD statement	Feldman¹⁰	Lok¹¹	Twine¹²	Bosanquet¹³
checklist				
Title		X	X	X
Abstract	X	X	X	X
Background		X	X	X
Source of data	X	X	X	X
Participants	X	X	X	X
Outcome	X	X		X
Predictors	X	X	X	X
Sample size	X	X	X	X
Missing data	X	X	X	
Statistical analysis	X	X	X	X
Risk groups		X		
Development/validation	X	X		
Participants	X	X		
Model development	X	X	X	X
Model specification	X	X	X	X
Model performance	X	X		
Model updating				
Limitations	X	X		X
Interpretation	X	X	X	X
Implications	X	X	X	X
Supplementary information				X
Funding	X	X	X	X

Table 3.1: Summary table for included studies in terms of fulfillment of TRIPOD statement

The number of participants included in the development of the prediction models was clearly reported in all four studies, ranging from 218 to 422 patients. (table 3.2) The prognostic predictive models included a median of five risk predictors. The most commonly identified risk predictors included age, venous diameter and CVD. Three models used multivariable regression model whilst the other two models used a series of separate univariable cox regression analyses. All studies clearly identified the type of statistical method that they used to derive the prediction model, two were derived using a Cox proportional hazards model (Twine et al, 2012; Bosanquet et al, 2015) and three models used logistic regression (Feldman et al 2003, Lok et al, 2006).

Study	Year	Country	Design	Study population	Outcome	Sample size	Predictors in the model	Method of validation	Type of model
Feldman (10)	2003	US	Prospective cohort study	ESRF patients >18	AVF maturation (yes/no)	348	Age, CVD, Previous access, BP, dialysis dependent, Heparin use, Vein diameter	Internal: Bootstrap	Multivariable logistic regression model / Generalised estimating equations
Feldman (10)	2003	US	Prospective cohort study	ESRF patients >18	AVF maturation (yes/no)	348	Age, CVD, Previous access, BP, dialysis dependent	Internal: Bootstrap	Multivariable logistic regression model / Generalised estimating equations
Lok (11)	2006	Canada	Prospective cohort study	ESRF patients >18	AVF non maturation (yes/no)	422	Age, PVD, CVD, Ethnicity	Internal: cross validation and bootstrapping and External	Multivariable logistic regression model
Twine (12)	2012	UK	Retrospective cohort study	ESRF Patients >18 Snuffbox fistulas	Time to Patency failure (yes/no)	218	Age, second contralateral procedure, venous diameter, CVD, CVA, Diabetes	None	A series of separate univariable Cox's proportional hazards regression
Bosanquet (13)	2015	UK	Retrospective cohort study	ESRF Patients >18 Forearm fistulas	Time to Patency failure	276	Central venous access, Age, Venous diameter, previous lower limb angioplasty, Absent intra-operative thrill	None	A series of separate univariable Cox's proportional hazards regression

Table 3.2: Summary table for included predictive models

All five studies claimed to have carried out some form of evaluation of the prediction

model. Three models (Feldman et al 2003, Lok et al, 2006) (60%) conducted an internal validation of the prediction model with bootstrapping, with one of them also using an internal cross validation and external validation (Lok et al, 2006), In our opinion two studies did not sufficiently assess their models to validate them. (Twine et al, 2012; Bosanquet et al, 2015)

Three studies (Lok et al, 2006; Twine et al, 2012; Bosanquet et al, 2015) (60%) derived simplified scoring systems from the risk prediction models. One study (Lok et al, 2006) derived a simple points system by rounding odds ratios to the nearest integer, whereby the resulting score would be a simple summation of the integers. One study (Twine et al, 2012) derived a simple scoring system by giving an integer of 1 for all significant variables however they did not actually use the hazard ratios from the cox model. The second study (Bosanquet et al, 2015) used a similar simple method, however decided to give two significant variables an integer of 2 due to their higher hazards ratio.

Parameters identified that were common to all scoring system were age and CVD (cardiovascular disease). Recent studies have confirmed both age and CVD as a risk factor in VA outcomes which supports both as potential prognostic markers (McGrogan et al, 2015)

Previous access was identified as a risk factor in two studies and specifically contralateral previous access. Venous diameter, a major factor in access planning was only noted in three models although studies assessing outcome using vein size less than a pre-defined threshold (e.g. <2mm cephalic vein at wrist) show a strong correlation with failure (Smith, Gohil and Chetter, 2012).

Dialysis dependency and BP was noted in two studies. Whilst studies subdividing patients into pre-dialysis and post dialysis AVF formation show better outcomes for

the former this may be confounded by multiple factors such as previous access attempts, central venous catheters, uraemia and overall clinical co-morbidity (Smith, Gohil and Chetter, 2012).

In access naïve patients AVF outcome was no different than in patients who had already started dialysis although in patients where access was created on the ipsilateral side as a previous CVC had worse outcomes. This is consistent with previous access being a parameter.

Ethnicity which has previously shown to affect outcome was only used in one study may reflect the low level of ethnic diversity in the studies rather than a true reflection of ethnicity as a risk (Lok et al, 2006)

Pre –existing disease such as diabetes was only a risk in one model although other markers of arterial disease (previous cerebrovascular accident /previous lower limb angioplasty/peripheral vascular disease) were used. The contribution of arterial factors to AVF outcome is poorly defined and more accurate measures may be required to enable inclusion in prognostic models.

One model used absent intra-operative thrill as a strong, but not unexpected marker of negative outcome.

3.5 DISCUSSION

Haemodialysis is a lifeline for end stage renal failure patients with vascular access being a major component of survival. Arteriovenous fistulas have been described as the gold standard due to its potential long-term patency, decreased rate of complications such as infection and overall survival benefit. (Dhingra et al, 2001) Despite this a major limitation of AVFs is the need for the vein to mature to a size large enough to be needled for haemodialysis. A number of factors have been associated with failure of maturation and this has been described widely in the current literature.(Smith, Gohil and Chetter, 2012) These include both patient and surgical variables.

In the general medical literature, scoring systems and predictive models have been widely recognized as useful tools in stratifying patients and predicting outcomes in cohorts of patients. In vascular access, the ability to predict successful maturation, or high risk of failure to mature may allow tailoring of clinical practice to individual patients and allow better planning of procedure and improved success. In common with many areas of vascular access where the current literature has little evidence there is a lack of available data on predictive models and this review could only find four eligible studies with a total of five models being described. This is a limitation to this review, although it does highlight a key area for future research. Only one paper was found to attempt to validate the available models, it would suggest that these are not widely used in clinical practice (Lilly et al, 2012). The lack of demonstration of validation and performance evaluation of these models on new populations makes it impossible to recommend these models. Further testing and validation by a different group of investigators in different patient cohorts is necessary. More advanced statistical approaches such as boot strapping to internally validate the predictive

model may be used.

A weakness of comparing these models is the heterogeneity of outcomes that were used in the available models in particular AVF maturation, AVF non-maturation or AVF patency. This is a typical problem in studies of vascular access as different and often non-standardized outcomes are commonly described in different studies making comparison challenging and recommendations for standard outcome measures is mandated (Sidawy et al, 2002)

The number of patients involved in the modelling process in the identified studies (n=218 to 422) compares poorly to available models on other topics such as end stage renal failure where numerous models used over 5000 patients (Collins et al, 2013). Compared to models used in other topics, those available to this review use few variables. The results of haemodialysis fistula maturation study (Dember et al, 2014) will hopefully yield more data for predictive modelling with a higher number of patients and potentially more predictive variables.

In conclusion this review has found a small number of predictive models in vascular access. The disparity between each study limits the development of a unified predictive model and therefore we recommend more research is required in this field. The utility of an accurate well-designed predictive model, which could be applicable to a clinical setting, would provide benefit in the planning and tailoring of vascular access for haemodialysis.

Chapter 4

**Validation study of the use of a portable
infrared thermal imaging camera for
temperature measurement by comparison to
standard methods of thermometry**

4.1 ABSTRACT

This study was designed to compare the temperature readings obtained from a newly available portable infrared thermal imaging camera (FLIR ONE - FLIR Systems Inc., Wilsonville, Oregon, USA) with more standard methods of thermometry.

Infrared thermal imaging was initially compared and found to correlate very well with both thermocouple and standard thermometer in a body of water with a changing temperature. It was subsequently compared and found to correlate well with both thermocouple and thermistor on measuring skin temperature.

In conclusion the results of this study confirms that the use of infrared thermal imaging is a valid, non-invasive and user friendly method of measuring skin temperature in humans and is comparable to more traditional methods of thermometry.

4.2 INTRODUCTION

The relationship between high temperature and illness was first described in cuneiform tablets from Mesopotamia over 3 millenniums ago. However it was not until the renaissance that scientists started to look into ways to measure temperature. In 1592 Galileo Galilei invented the first documented device to show changes in temperature, a thermoscope (Anbar, Gratt and Hong, 1998). A thermoscope could show differences in temperature, allowing observers to know if something was getting hotter or colder. However, the thermoscope could not provide an exact temperature reading as there was no numerical scale. A German physicist Daniel Gabriel Fahrenheit invented both the mercury and the alcohol thermometer at the beginning of the 18th century (Haller, 1985). Fahrenheit's mercury thermometer consisted of a capillary tube filled with mercury. The mercury expands or contracts as the temperature rises or falls. Alongside his inventions, he also described a temperature scale which has the freezing point of water at 32 degrees Fahrenheit (°F) and the boiling point at 212 °F. Soon after Fahrenheit, a Swedish astronomer Anders Celsius came out with a different type of temperature scale, which is today referred as the Celsius scale (Pearce, 2002). The original scale set 0°C as the boiling point of water and 100°C as the freezing point, but he flipped it around soon after inventing the scale. The term Celsius was adopted in 1948 by an international conference on weights and measures and is the preferred scale internationally, apart from the United States where Fahrenheit is still commonly used (Stimson, 1949). This puts the boiling and freezing points of water exactly at 100 degrees apart, compared to 180 in the Fahrenheit scale. This is why it is sometimes referred to as the centigrade scale.

Thomas Seebeck, a german physicist, discovered in 1821 that a magnetic field can

be observed when there is a temperature difference between the joints of two different metals (Velmre, 2007). The magnetic field he discovered was later shown to be due to thermo-electric current, which can be used to measure temperature. This technique, thermocouple, was found to be less easy to use than thermometers but more accurate especially at extreme temperatures. There are also potential limitations to thermocouples such as calibration, contact reliability and effect of it on skin temperature (Harper Smith et al, 2010).

Thermistors are based on a piece of ceramic with a known resistance that fluctuates with temperature (Moran and Mendal, 2002). Depending on its size, the thermistor usually has a longer response time compared to thermocouples. Similarly to thermocouples, they have limitations such as the influence of shape and contact pressure and the cover to hold the sensor onto the skin (Harper Smith et al, 2010).

This study was designed to compare the temperature readings obtained from a newly available portable infrared thermal imaging (FLIR ONE - FLIR Systems Inc., Wilsonville, Oregon, USA) with more standard thermometry. This was carried out to assess the suitability and efficacy of the product prior to its use in a clinical setting. Infrared thermal imaging cameras have previously been used in clinical context but these were complex to use and large in size. Technical advances in both software and hardware have improved dramatically over the last decade. Today's IRTI cameras are easy to use, cost effective and considerably more portable. However they are yet to be tested in a clinical setting.

4.3 METHOD

Experiment 1

Infrared thermal imaging camera

The FLIR ONE (FLIR Systems Inc., Wilsonville, Oregon, USA) portable infrared thermal imaging camera was used for our study. The thermal camera was kept perpendicular to the plane of acquisition as angles of measurement of up to 20 degrees have a negligible effect on the acquired thermographic temperatures. The camera takes full spectrum images where each image pixel acts as a spot measure of temperature, which is directly proportional to the thermal energy emitted by that site. Subsequent analysis using the accompanying FLIR software for Mac OS X allows measurement of spot temperatures or mean temperatures over selectable area.

Standard thermometry

For thermometry, we used two different probes to assess temperature. A standard thermometer was used for assessment. It is a tall, narrow glass column with a constant cross-sectional area, which contains thermometric liquid (red spirit). As the temperature of the thermometric liquid in a thermometer increases, its volume increases and the increase in volume is proportional to the increase in temperature. A digital thermometer was also used for surface thermometry. It is based on K-type thermocouple sensor which is a device consisting of two conductors that contact each other. A thermocouple produces a voltage when the temperature of one of the contact points differs from the temperature of another, in a process known as the thermoelectric effect.

Procedure

Testing was performed in the same examination room at a temperature of 20°C which was monitored using a calibrated thermometer. A standard liquid thermometer and a thermocouple sensor were placed in a bowl full of water. In the first test, boiling water was poured into the bowl and temperature readings were taken at regular intervals using both types of thermometry. The intervals were determined by temperature change in the liquid thermometer (5 degree decrease intervals). In the second test, freezing water was poured into the bowl and temperature readings were taken at regular intervals using both types of thermometry. The intervals were determined by temperature change in the liquid thermometer (2.5 degree increase intervals). Infrared thermal imaging were taken at each interval.

Analyses

Infrared thermal imaging temperature measurements were obtained using the FLIR software and these were recorded on an excel spreadsheet alongside standard thermometer and thermocouple temperature measurements. The data recorded was then analysed statistically using simple linear regressions, to measure the strength of the relation between measurements made by the infrared thermal imaging camera and those made using the different types of thermometry.

Experiment 2

Infrared thermal imaging camera

The FLIR ONE (FLIR Systems Inc., Wilsonville, Oregon, USA) portable infrared thermal imaging camera was used for our study. The thermal camera was kept perpendicular to the plane of acquisition as angles of measurement of up to 20

degrees have a negligible effect on the acquired thermographic temperatures. The camera takes full colour images where each image pixel acts as a spot measure of temperature, which is directly proportional to the thermal energy emitted by that site. Subsequent analysis using the accompanying FLIR software for Mac OS X allows measurement of spot temperatures or mean temperatures over selectable area.

Skin thermometry

For thermometry, we used two different probes to assess skin temperatures. A Philips skin surface probe (21078A) was used with Philips V26C monitoring system. The temperature measurement is based on a thermistor whose resistance is inversely proportional to its temperature. By measuring the thermistor's resistance, its temperature can be calculated. The resistance of the thermistor is measured by passing a current through it and measuring the voltage developed across it. A digital thermometer was also used for surface thermometry. It is based on K-type thermocouple sensor which is a device consisting of two conductors that contact each other. A thermocouple produces a voltage when the temperature of one of the contact points differs from the temperature of another, in a process known as the thermoelectric effect

Subjects

A total of ten volunteers (four females, six males) participated in a series of skin temperature measurement. All were healthy young adults aged between 21 and 32 years of age (mean: 24.2y) and were right handed. All gave informed consent to participate in the study, which was approved by the University of Birmingham (ERN: 15-0890).

Procedure

Subjects were seated in a quiet environment. Both hands were rested on a specially designed pillow to allow resting of the arms. The volunteers were allowed to acclimatize to the environment and room temperature for a period of five minutes. Testing was performed in the same examination room at a temperature of 20°C which was monitored using a calibrated thermometer. The areas assessed for skin temperature were the palms and forearms bilaterally. Participants were also asked to avoid using hand cream, moisturiser or other cosmetics that could affect the thermography.

A spot was marked on each area of interest. Infrared thermal images were taken of both palms and forearms. Subsequently the skin temperature probes were attached to the skin of each area on the mark in turn: left palm, left forearm, right palm and right forearm. These different sites were chosen to assess the applicability of the measurement methods to areas where vascular access surgery would take place. Once the temperature for both methods had stabilized, these were recorded in a spreadsheet.

Analyses

Infrared thermal imaging temperature measurements of the marked spots were obtained using the FLIR software and these were recorded on an excel spreadsheet alongside thermistor and thermocouple temperature measurements. The data recorded was then analysed statistically using simple linear regressions, to measure the strength of the relation between measurements made by the infrared thermal imaging camera and those made using the different types of skin thermometry.

4.4 RESULTS

Experiment 1

This experiment was designed as to avoid the limitations of contact pressure and reliability as the probes were fully immersed in the water. Infrared thermal imaging was found to correlate very well with both standard thermometer and thermocouple. In the boiling water test, IRTI was found to have a pearson correlation coefficient r value of 0.99 with both (Figure 4.1), P -value <0.05 . Similarly in the freezing test, IRTI was also found to have a pearson correlation coefficient r value of 0.99 with both (figure 4.2), P -value <0.05 .

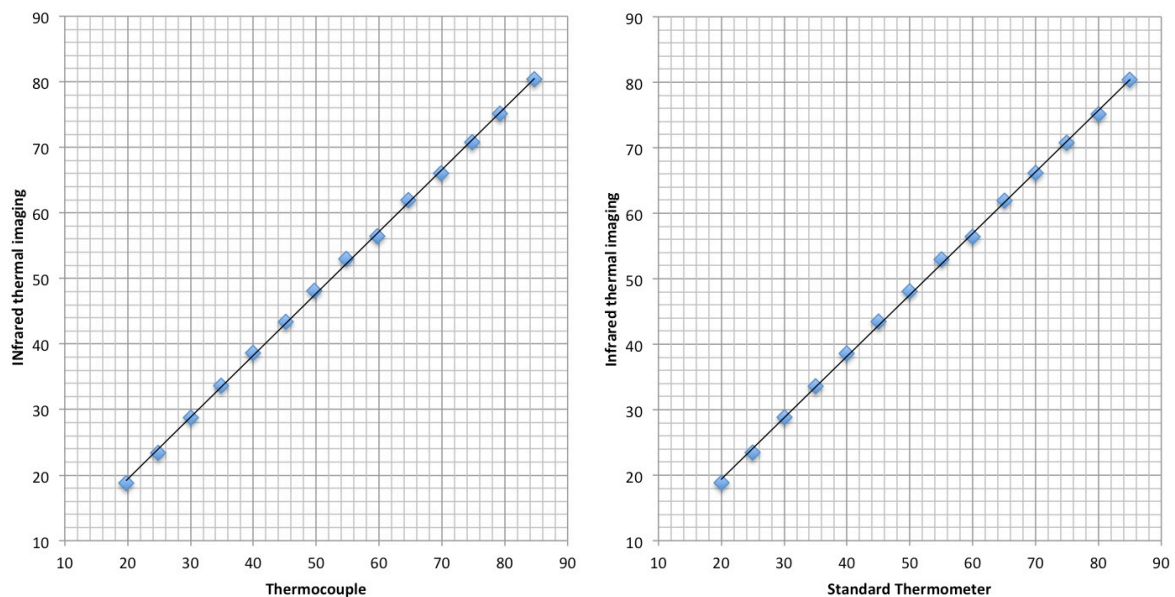


Figure 4.1: Comparison of infrared thermal imaging with both thermocouple and standard thermometer during the boiling water test

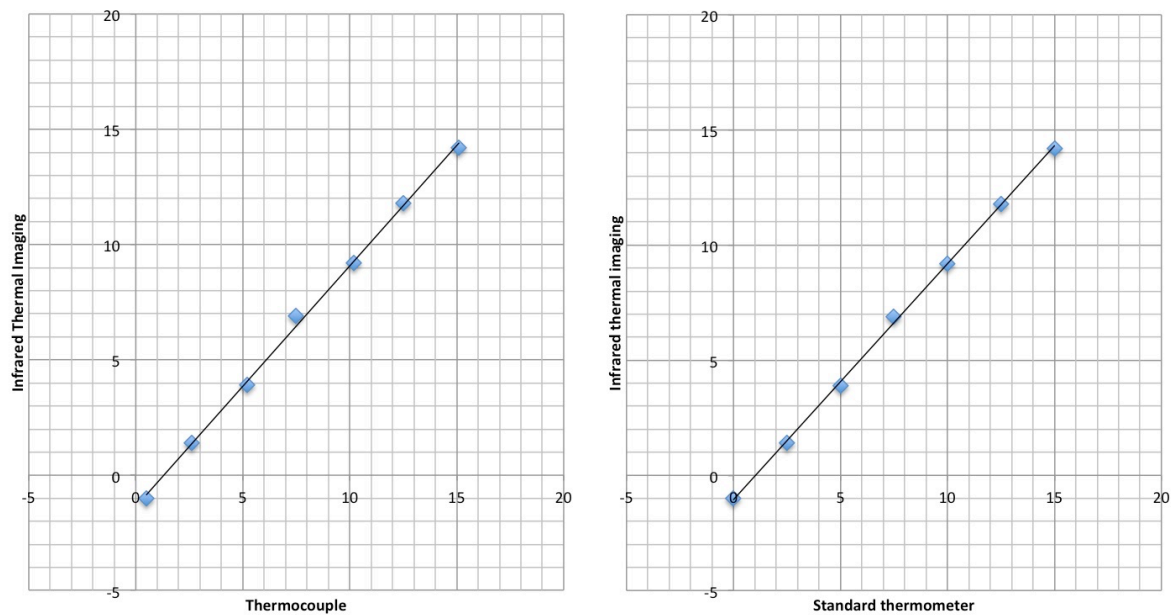


Figure 4.2: Comparison of infrared thermal imaging with both thermocouple and standard thermometer during the freezing water test

Experiment 2

To avoid potential errors in methodology by multiple researchers, a single researcher collected the data using a consistent methodology. The procedure was designed to measure the emitted surface body heat of the volunteer at multiple anatomical points. In the ten healthy volunteers, each thermometry device took 40 temperature readings. IRTI was found to correlate with both thermocouple and thermistor. Compared to thermocouple IRTI had a pearson correlation coefficient r value of 0.79 and 0.84 when compared to thermistor (Figure 4.3), P -value <0.05 .

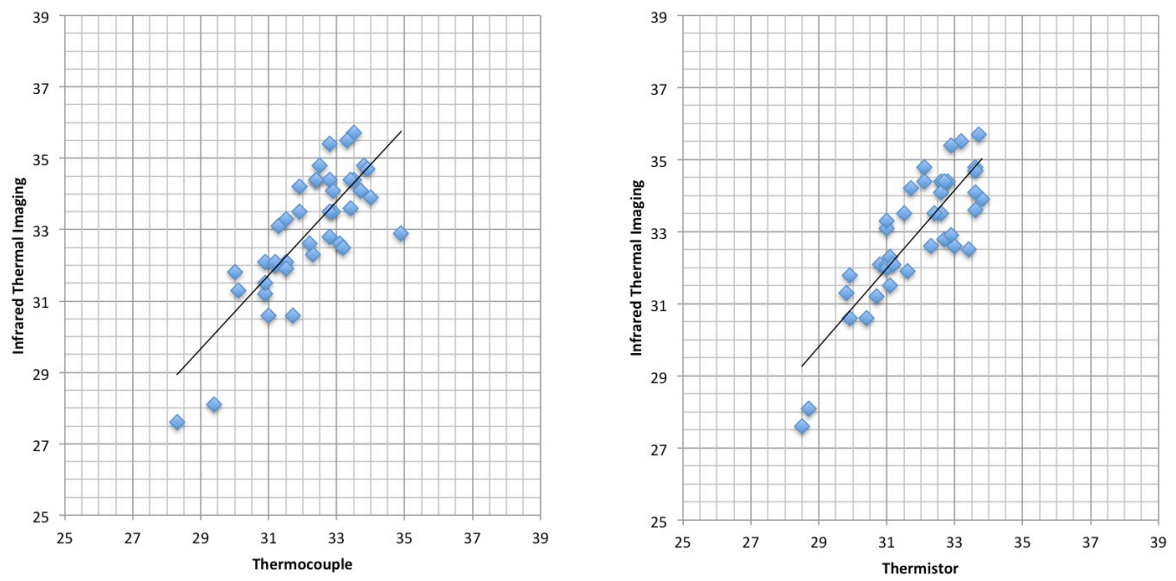


Figure 4.3: Comparison of infrared thermal imaging with both thermocouple and thermistor in experiment 2

4.5 DISCUSSION

The main finding of the current study was a positive correlation between infrared thermal imaging and more traditional methods of measuring temperature. In experiment 1, we showed that IRTI had near perfect correlation with both thermometer and thermocouple when measuring the temperature of a body of water. The temperature from IRTI was slightly lower when the water was cooling down from a boiling temperature as it represented the surface whilst the other two methods were immersed in the water and therefore representing the core temperature.

The relationship between core body temperature and peripheral skin temperature is complex and varies both within and between subjects. However experiment 2 demonstrated that infrared thermal imaging can reliably reflect skin temperature. There was a positive correlation between infrared thermal imaging and both thermocouple and thermistor. The temperature from IRTI was slightly higher than the other two methods of thermometry. This could be due to a margin of error with the traditional methods in view of contact pressure limitations.

In conclusion the results of this study confirms that the use of infrared thermal imaging is a valid, reliable and user friendly method of measuring skin temperature in humans and is comparable to more traditional methods of thermometry.

Chapter 5

**Analysis of infrared thermal imaging as a
marker of tissue perfusion: Vascular occlusion
test with a comparison to near infrared
spectroscopy**

5.1 ABSTRACT

The use of infrared thermal imaging to diagnose circulatory problems in the hands is based upon the assumption that a change in skin temperature can be related to a change in skin blood flow and the vascular supply is equal in both upper limbs. In this study 30 healthy volunteers were exposed to a 2 min vascular occlusion test. The resultant reactive hyperaemia with associated skin erythema was assessed with Infrared thermal imaging (IRTI) and near infrared spectroscopy (NIRS) to measure palmar temperatures and mixed arteriovenous oxygenation of both occluded and non occluded arms. We found IRTI to be a useful tool in quantifying reactive hyperaemia. Interestingly we also found that there was an increase in palmar temperature on the non-occluded side, which would suggest a neurovascular reactive response to the vascular occlusion test.

5.2 INTRODUCTION

Endothelial dysfunction has been described as the inability of the artery to sufficiently dilate in response to an appropriate endothelial stimulus. It can be assessed by the measurement of flow-mediated dilatation (FMD) of the brachial artery after occlusion of the blood flow. It is thought that the main mechanism inducing FMD is an increase in shear stress, which subsequently leads to a release of nitric oxide from the endothelium (Betik, Luckham and Johnson, 2004). The released nitric oxide causes blood vessel dilatation (Betik, Luckham and Johnson, 2004). FMD is assessed in a noninvasive manner using high-resolution ultrasound of the brachial artery and has been proven to be a useful clinical tool to assess endothelial dysfunction, which in turn is a predictor of cardiovascular disease (Green et al, 2011). However, FMD is operator dependent, technically challenging and requires extensive training (Flammer et al, 2012). FMD is also only measured on one arm. Therefore it is likely that systemic haemodynamics, such as those resulting from alterations in the autonomous nervous system tone, are not accounted for.

Infrared thermal imaging (IRTI) has been used for several decades to monitor cutaneous temperature distribution (Terminology Commission of European Association of Thermology, 1978). The technology behind infrared thermal imaging has developed considerably since its introduction in the mid 20th century. Technical advances in both software and hardware have improved dramatically over this time. Today's IRTI cameras are reliable, accurate, cost effective and considerably more portable than previously (Fernandes et al, 2012; Vargas et al, 2009). Endothelium-mediated changes in tone leading to dilatation after occlusion of the brachial artery

are reflected with a hyperaemic response distally. This response should result in a change of cutaneous temperature of the hand.

Infrared light has the unique ability to penetrate beyond the skin into deeper tissues. Equally, infrared light absorption by haemoglobin and myoglobin is relatively low allowing a significant amount of light to pass through tissues. This relative transparency of infrared light is utilised by near infrared spectroscopy (NIRS) (Lipcsey, Woinarski and Bellomo, 2012). It can measure tissue oxygenation by the use of adhesive pads, which emit a near infrared light at two specific wavelengths that penetrate the tissue allowing the receiver to pick up the amount of light passing through the tissue (Boushel and Piantadosi, 2000; Creteur, 2008). This allows differentiation of oxygenated and deoxygenated haemoglobin measured in pulsatile and nonpulsatile blood contained within venous, arterial and capillary vessels (Ferrari, Mottola and Quaresima, 2004). This noninvasive technique can be performed at the bedside and provides accurate tissue oxygen saturation readings.

In this study, we aimed to investigate the use of infrared thermal imaging in assessing changes in cutaneous temperature of both hands following a vascular occlusion test and in a subset of patients to compare it to near infrared spectroscopy.

5.3 METHODS

This study was done at the University Hospital Birmingham and received full ethical approval from the University of Birmingham (ERN: 15-0890). Written informed consent was obtained from all healthy volunteers.

Infrared thermal Imaging

Both hands were imaged at the same time with a portable thermal camera (FLIR ONE, FLIR Systems Inc., Wilsonville, Oregon, USA). Images were taken at 15 second intervals for a total of five minutes (1 minute rest period, 2 minutes occlusion period and 2 minutes reperfusion period). Thermal images were subsequently processed to extract mean temperature of the palm for both hands at each time interval (Figure 5.1). Measurements on the non-occluded hand were used to control for concurrent non-endothelium dependent changes in vascular tone.

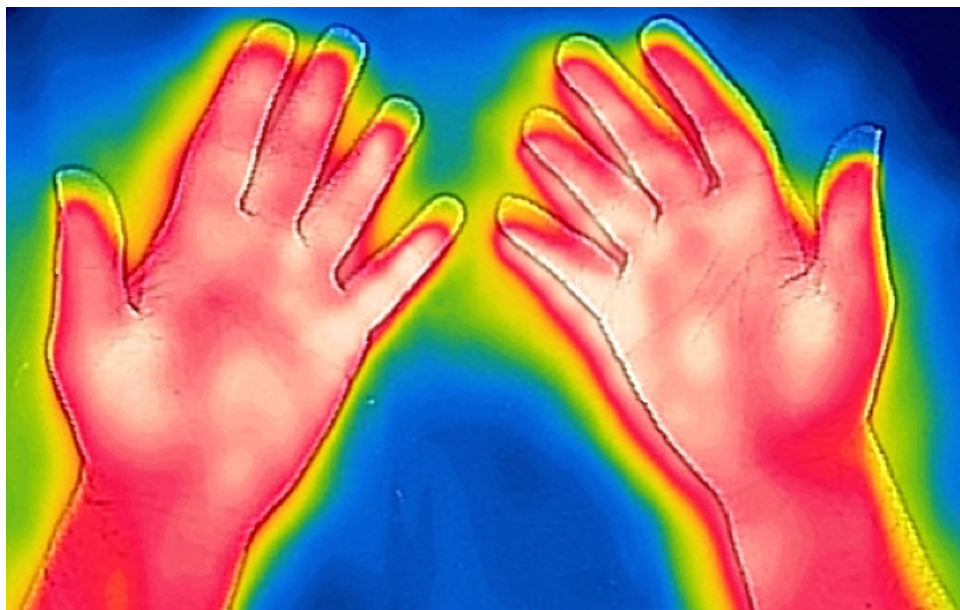


Figure 5.1: Infrared Thermal Imaging of both hands

Near infrared spectroscopy

NIRS was measured using the INVOS™ cerebral/somatic oximeter using an adult probe to the thenar eminence of both the dominant and non-dominant arms. This gives a non-invasive real time measurement of tissue oxygen saturation. The sensor assesses oxygen saturations in both the venous and arterial system in a 3:1 ratio to yield a result. Measurements were recorded at 15 seconds interval for a total of five minutes (1 minute rest period, 2 minutes occlusion period and 2 minutes reperfusion period). The minimal reading achieved is 15% and maximum is 95% for the machine.

Vascular Occlusion Test

Subjects were seated in a quiet environment. Both hands were rested on a specially designed pillow to allow resting of the arms (Figure 5.2). The volunteers were allowed to acclimatize to the environment and room temperature for a period of five minutes. An initial manual blood pressure and heart rate measurements were taken on the non-dominant arm. Following a rest period, the sphygmomanometer was then rapidly inflated until 30 mmHg above the systolic pressure and kept inflated for a two minute period. The cuff was then released to allow reperfusion.

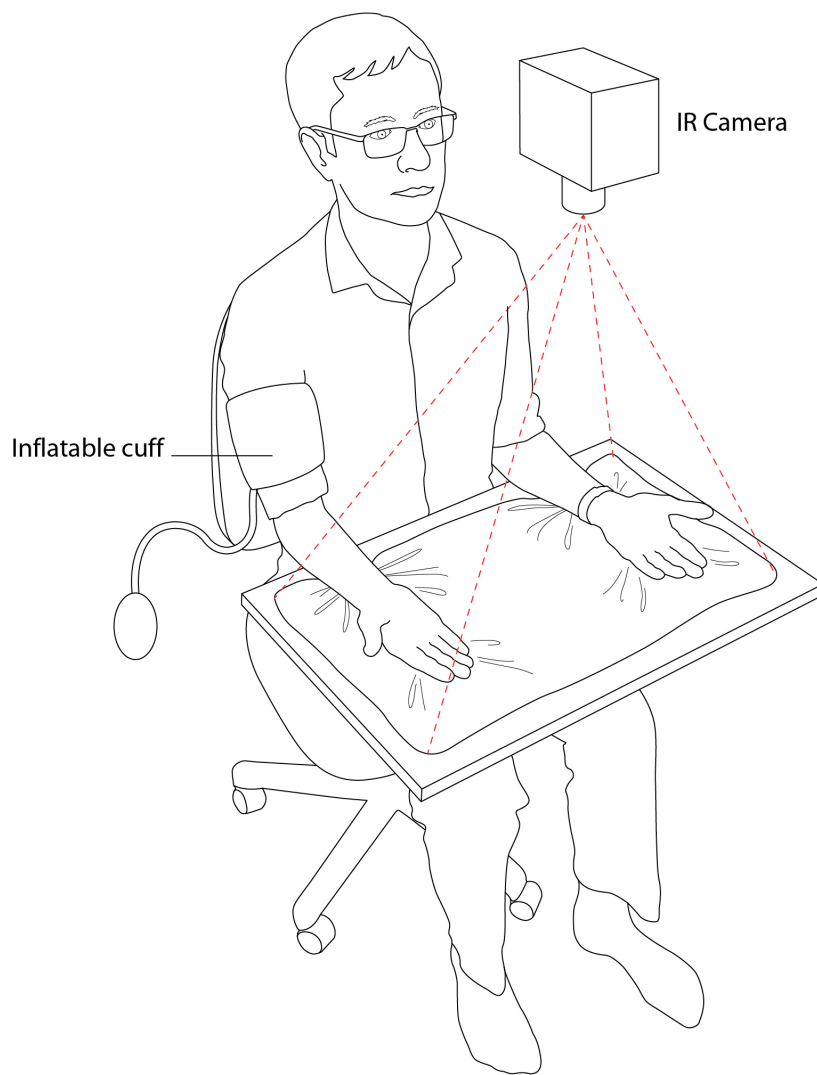


Figure 5.2: Illustration showing the setting for the vascular occlusion test

Statistical Analysis

Mean palmar temperature was calculated for both occluded and non-occluded. All temperature measurements were taken in degree celcius. Data was compared using paired Student's t-test (Zimmerman and Donald, 1997). Results were expressed as a mean. Statistical significance was considered at a probability of $p < 0.05$. Statistical analyses were performed using SPSS.

5.4 RESULTS

Thirty healthy volunteers were included in the initial study. The mean age was 33.8y (SD:±8.6). Clinical, thermal and haemodynamic characteristics of the volunteer cohort are described in table 5.1. At baseline there was a significant difference between mean dominant and non-dominant hand temperatures (p-value<0.05) with the dominant side being warmer.

Characteristics	Healthy volunteer cohort N=30
Mean Age	33.8 ± 8.6
Sex	12M:18F
Ethnicity	Caucasian 66% Asian 20% Other 14%
Smokers	8
Non dominant hand	5R:25L
SBP	119±8
DBP	74±7
MAP	89±6
HR	74±9
Mean dominant hand temperature	32.6 degrees
Mean non dominant hand temperature	32.3 degrees

Table 5.1 Volunteer demographics, haemodynamic and thermal characteristics of the 30 healthy volunteers for the vascular occlusion test

Mean temperature of both hands at the different time point of the study are described in Figure 5.3, blood pressure cuff was inflated at time point 4 and released at time point 12. Typical IRTI changes seen at the different periods of the study are described in figure 5.4. Once the blood pressure cuff was inflated, the occluded side temperature began to drop. Interestingly the mean temperature of the non-occluded

side began to rise significantly as the vascular occlusion was initiated (p-value<0.05) and this rise was enhanced after the cuff was released (p-value<0.05). On the occluded side, we noted a sharp significant rise in hand temperature following release of the occlusion, consistent with a reactive hyperaemic response (p-value<0.05). The changes in mean temperature at different time points of both hands are described in table 5.2.

Experimental times	Mean temperature (95% CI):	Mean temperature (95% CI):
	occluded hand	non occluded hand
Time point 1: rest period	32.3 \pm 1.3	32.6 \pm 1.3
Time point 13: peak occlusion period	31.9 \pm 1.2	33 \pm 1.3
Time point 21: peak reperfusion period	33.5 \pm 1.3	33.7 \pm 1.4

Table 5.2: Mean palmar temperature during rest, peak occlusion and peak reperfusion periods

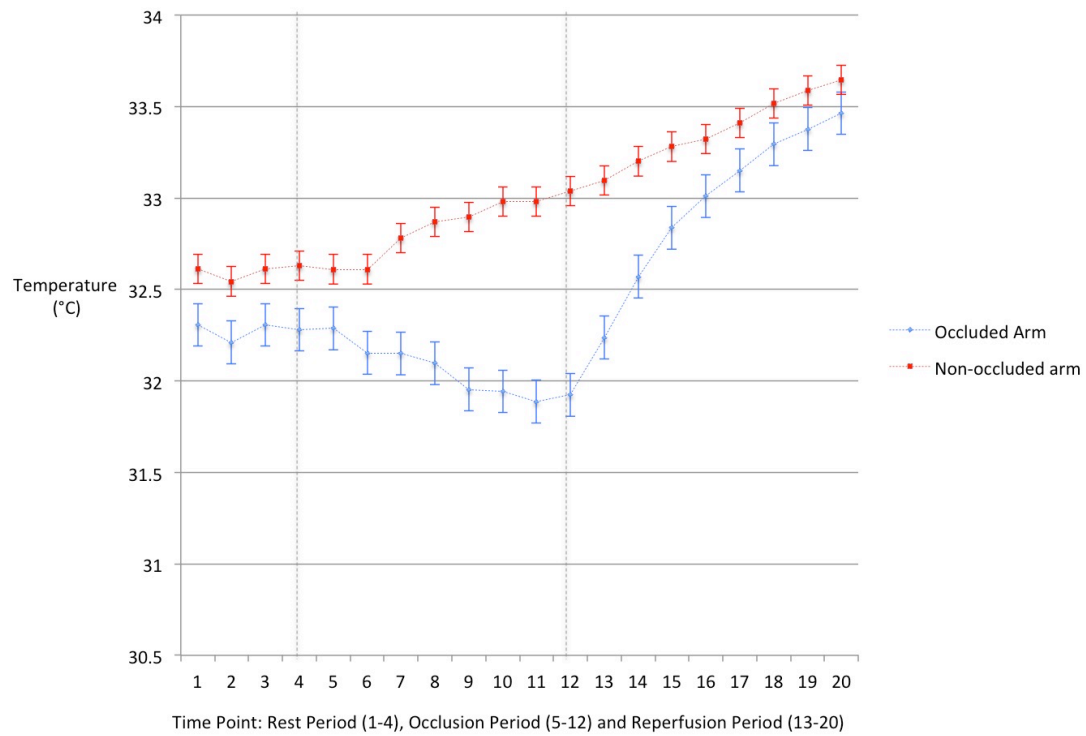


Figure 5.3: Time course of mean changes in palmar temperatures before, during and after the vascular occlusion test for both occluded and non-occluded arms

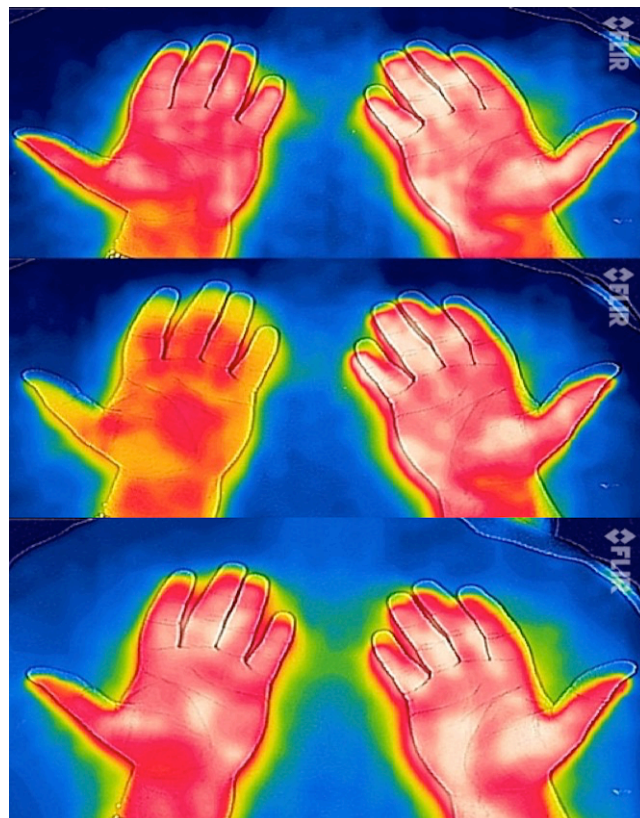


Figure 5.4: Typical thermal changes seen during the three different periods of the vascular occlusion test

Following preliminary assessment of the IRTI results, a subset of the healthy volunteers (n=10) underwent additional INVOS assessment during the vascular occlusion test. At baseline there was a significant difference between mean dominant and non-dominant tissue oxygen saturation (StO₂) (p-value<0.05) with the dominant side being higher. Mean StO₂ of both hands at the different time point of the study are described in Figure 5.5, blood pressure cuff was inflated at time point 4 and released at time point 12. Once the blood pressure cuff was inflated, the occluded side StO₂ began to drop as expected (p-value<0.05). Interestingly the mean StO₂ of the non-occluded side began to rise as the vascular occlusion was initiated (p-value<0.05) and this rise continued after the cuff was released (p-value<0.05). On the occluded side, we noted a sharp significant rise in StO₂ following release of the occlusion (p-value<0.05).

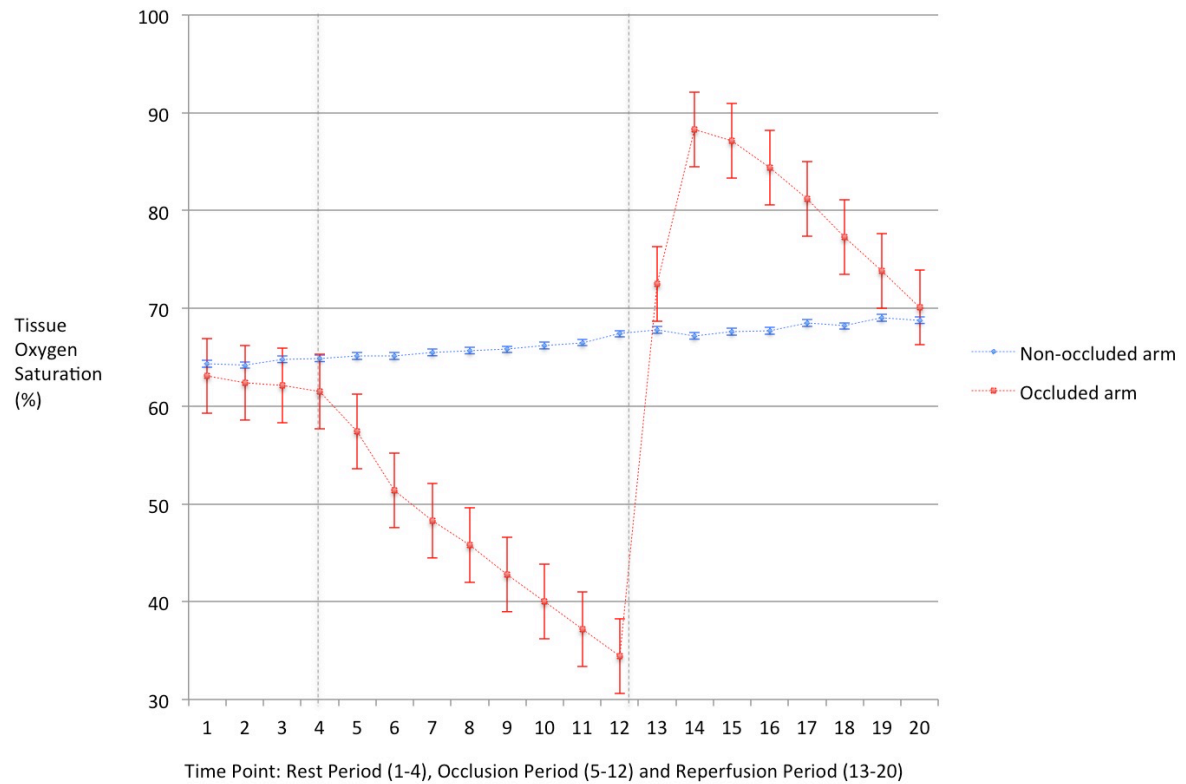


Figure 5.5: Time course of mean changes in tissue oxygenation before, during and after the vascular occlusion test for both occluded and non-occluded arms

5.5 DISCUSSION

The principal finding of this study is that infrared thermal imaging can be used to quantify reactive hyperaemia following a vascular occlusion test. In addition IRTI can also show clearly those changes through the images taken at different time points.

As expected, a vascular occlusion test leads to a decrease in palmar hand temperature in the occluded side. This is due to a lack of blood perfusion of distal tissues. We assessed palmar temperature which is the warmest part of the hand and therefore we expect this drop in temperature to be even more emphasised in the most distal parts such as the tip of the fingers. The release of the blood pressure cuff led to a reactive hyperaemic response. This response has been investigated in the past and is believed to be caused by nitric oxide release from localised vascular endothelium. This response has been measured with flow mediated dilatation and has been shown to be a good assessment of endothelium function. This in turn has been a clinically useful tool in the prediction of cardiovascular events. Therefore IRTI might also be a useful measure of endothelium function as it can quantify reactive hyperaemia. However we would require large studies with concurrent FMD measurements to definitively prove this. Possible study limitations include the 2-minute cuff inflation compared to the traditional 5-minute protocol for vascular function assessment. However, an excellent correlation of vascular function between 2-minute and 5-minute arm cuff occlusions, has been demonstrated in the literature (Gul et al, 2009; Yvonne-Tee, 2008).

Interestingly we found a significant change in temperature of the contralateral side during both occlusion and reperfusion periods. To our knowledge, this increase in temperature has only been described in one other study in the literature.¹² This rise

in palmar temperature is likely due to a neurovascular reactive response mediated by the autonomic nervous system leading to vasodilation and therefore an increase in blood flow (Ahmadi et al, 2009). In addition, there would also be diversion of blood flow from the occluded side into the non-occluded side during the occlusion period. This finding was also confirmed on near infrared spectroscopy as it showed an increase in tissue oxygenation on the contralateral side during a vascular occlusion test. This finding can correlate with an increase in blood supply to the contralateral side. It would be important to confirm those infrared thermal imaging results in a larger study with the addition of flow mediated dilatation and near infrared spectroscopy. If these results are confirmed in larger studies, it might well question the theory that reactive hyperaemia is only mediated by locally released factors.

Chapter 6

**A prospective observational study on the use
of infrared thermal imaging to predict
arteriovenous fistula outcomes: IRTIVA Study**

6.1 ABSTRACT

The arteriovenous fistula is the preferred method of long-term haemodialysis. However it has been shown to have a substantial rate of maturation failure. The formation of an AVF creates haemodynamic changes to blood flow in the arm with diversion of blood away from the distal circulation into the low pressure venous system, in turn leading to thermal changes distally. In this study we aimed to assess the novel use of infrared thermal imaging as a predictor of arteriovenous maturation. A prospective cohort study was conducted on 100 consecutive patients who had AVF formation from December 2015 to June 2016. Infrared thermal imaging was undertaken pre- and post-operatively on the day of surgery to assess thermal changes to the arms and assess them as predictors of clinical patency and functional maturation.

For clinical patency, infrared thermal imaging was found to have a positive predictive value of 88% and a negative predictive value of 86%. For functional maturation, it was found to have a positive predictive value of 84%, a negative predictive value of 95%. In addition, it was shown to have superiority to the commonly used intra-operative predictor of thrill as well as other independent pre-operative patient factors. Infrared thermal imaging has been found to be a very useful tool in accurately predicting fistula patency and maturation.

6.2 INTRODUCTION

The arteriovenous fistula (AVF) is the preferred method of long-term haemodialysis vascular access, as it has been shown to have better longevity and fewer complications than arteriovenous grafts (National Kidney Foundation, 2006). However, one of the major setback to AVFs is its substantial rate of failure to mature, which has been quoted to be as high as 50% (Dember et al, 2008).

Over the last few decades, numerous studies have tried to establish an association between AVF maturation and both pre-operative and intra-operative factors that will make it possible to predict the outcome of a newly created fistula (Farber et al, 2016). Predictive models based on patients' demographics and those factors have been suggested; however they are few in numbers, based on relatively small number of patients and associated with complex statistical and validity issues (Al Shakarchi et al, 2016c). Therefore currently intra-operative thrill is still the most commonly used predictor of AVF maturation.

The formation of an AVF creates haemodynamic changes to blood flow in the arm with diversion of blood away from the distal circulation into the low pressure venous system (Inston et al, 2017). Computational fluid dynamics (CFD) simulations have shown that immediately after AVF formation, the greater part of the arterial flow enters into the vein (81%) and only a smaller part flows through the distal artery (19%) toward the hand (Ene-Iordache and Remuzzi, 2012). Previous studies have shown that most of those changes occur in the first 24 hours following surgery (Yerdel et al, 1997; Lin et al, 1998). It has also been demonstrated in numerous studies that higher intra-operative blood flow in the AVF is associated with improved rates of maturation (Johnson et al, 1998). Therefore intraoperative blood flow

measurement has been proposed as a good predictor of AVF outcome, however it might have some accuracy issue as seen by the wide range of cut off values from the published literature (Berman et al, 2008; Lin et al, 2008; Saucy et al, 2010).^{10,11,12}

The post-operative haemodynamic changes causes a reduction in blood flow and perfusion distal to the anastomosis, which in turn should lead to a reduction in skin temperature until arterial remodeling occurs. This would propose a hypothesis that thermal changes, which occur distal to the anastomosis of an AVF, might be predictive of subsequent patency and maturation.

Infrared thermal imaging (IRTI) has been used to study a number of diseases where skin temperature can reflect the presence of inflammation in underlying tissues, or where blood flow has changed due to a clinical abnormality. IRTI has been shown to be equal to or superior to that of the traditionally used skin thermistor thermometry (Burnham, McKinley and Vincent, 2006). However the use of this technology was restricted to research purposes due to its high cost and complex use. Technical advances in both software and hardware have improved IRTI cameras dramatically as they are now more accurate, easy to use, and considerably more portable than previously providing a potential near patient tool for skin perfusion. The FLIR One camera is a lightweight, affordable and easy to connect attachment to a smartphone, whilst the provided software allows easy extraction of spot temperatures, which can be done directly from the smartphone or from a computer.

This study aimed to assess the novel use of infrared thermal imaging as a predictor of arteriovenous patency and maturation.

6.3 METHODS

The study was approved by University Hospital Birmingham and the National Research Ethics Committee (IRAS project ID: 186081). This was a prospective cohort study of consecutive eligible patients with chronic kidney disease. Recruitment was undertaken from December 2015 and June 2016 and patients were followed up until December 2016. All patients undergoing AVF formation were screened for the inclusion criteria and if appropriate, approached to participate in the study. All patients gave written informed consent on the day of surgery.

Inclusion criteria for the study were: consecutive patients undergoing arteriovenous fistula formation, aged over 18 years and able to consent. They had already started or were expected to progress to treatment with maintenance haemodialysis within 3 months. Exclusion criteria were: history of ipsilateral upper limb revascularization procedure, sympathectomy or complex vascular access procedure (arteriovenous graft and redo surgery).

All patients underwent pre-operative ultrasound mapping to select the most appropriate anatomical site dictated by vessel diameters. At our institution, a minimum diameter of 2mm for both artery and vein is required for fistula creation. Demographic and clinical data were collected including gender, age, cause of end stage renal failure, co-morbidities, type of AVF created, pre-operative ultrasound results and intra-operative finding including thrill. The presence of thrill was assessed at the conclusion of the procedure

Infrared thermal imaging assessment

Patients were seated in a quiet environment and were allowed to acclimatize to the environment and room temperature. Both hands were placed on a pillow to allow resting of the arms. Both arms were imaged at the same time with a portable thermal camera (FLIR ONE, FLIR Systems Inc., Wilsonville, Oregon, USA). This was carried out pre- and post-operatively within 30 minutes of the surgery (figure 6.1). The camera has a temperature sense range of -20° to 120° degrees celcius with an accuracy of 0.1° . Thermal images were subsequently processed to extract spot temperature at the tip of the middle finger on both hands, as this is the most distal part of the hand and should theoretically be the most affected by any haemodynamic change in blood flow. In each case, the measurements of the contralateral side were used as control. This is due to skin temperature being variable and inaccurate due to environmental factors if assessed as an absolute figure. Therefore, a more accurate way to measure skin temperature changes following AVF creation is to look at relative difference in temperature between operated and contralateral side before and after surgery. The measurements from the operated side were converted into relative temperatures by subtracting measurements made on the patient's contralateral side. The changes in relative temperatures from pre- to post-op were then calculated from the resulting values.

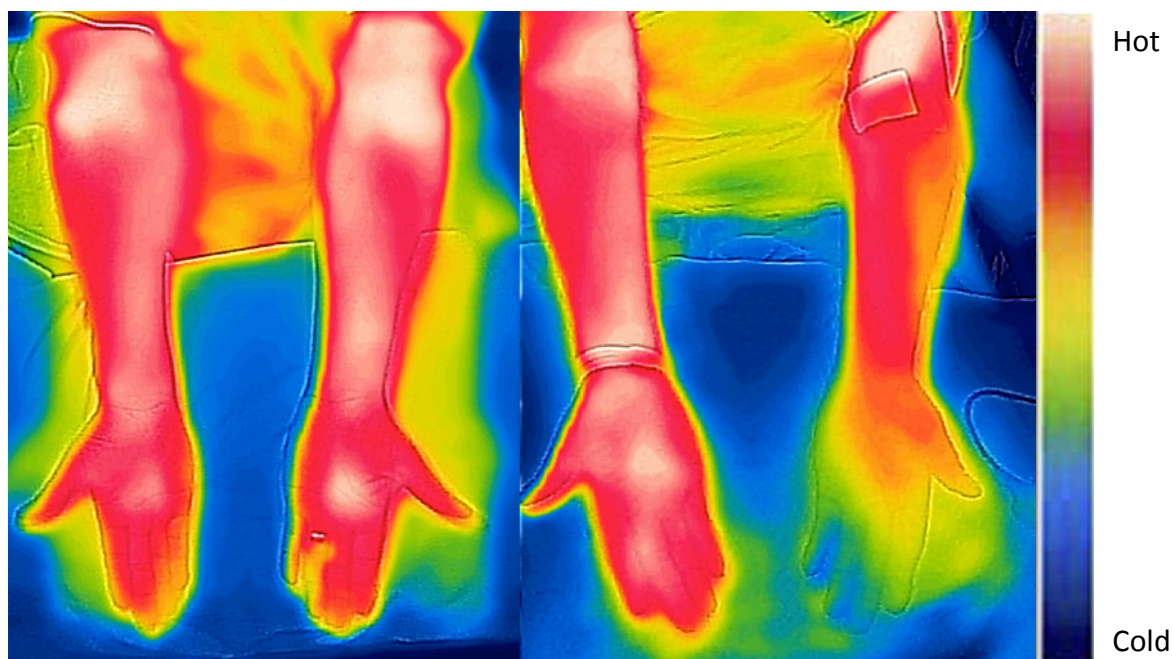


Figure 6.1 – Infrared thermal imaging on the same day before (left image) and after creation (right image) of a left brachiocephalic fistula, which matured successfully. (white = hottest, blue = coldest)

Outcome measure

The primary outcome measure for the study was AVF clinical patency. Post-operative fistula assessment was performed at 6 weeks after creation, to evaluate the status of the fistula. Clinical patency was determined with ultrasound criteria of AVF diameter > 6 mm and clinical assessment by an experienced clinician of the presence of a strong thrill at the anastomosis and suitability for needling. Clinical assessments done at 6 to 8 weeks post creation have been shown to predict the ability of the AVF to support dialysis with a mature functional AVF (Robbin et al, 2002). The secondary outcome measure was functional maturation as defined by successful successive catheter free dialysis with two needles.

Statistical analysis

Initially, comparisons were made between those patients whose fistulas did and did not mature. Continuous variables were reported as mean \pm SD, with p-values from independent samples t-tests, with Fisher's exact tests for nominal factors. Continuous factors that were found to be significantly associated with fistula maturation were further assessed using ROC curves, and the optimal cut-off values identified. Performance measures were then calculated for the predictive accuracy at these cut-off values, as well as for the nominal variables.

A multivariable binary logistic regression model was then produced, to test whether combining factors together into a risk score could give more accurate prediction of fistula maturation than was achieved by individual factors. A forwards stepwise approach was used to select factors for inclusion.

All analyses were performed using IBM SPSS 22 (IBM Corp. Armonk, NY), with $p < 0.05$ deemed to be indicative of statistical significance throughout.

6.4 RESULTS

Data were available for 100 consecutive patients with no patients being excluded. No patients received any intervention on their fistula to aid maturation. In two cases, the outcome of fistula maturation was not available, due to death ($n=1$) and complication leading to ligation ($n=1$) prior to follow up; hence these patients were excluded from further analysis. The remaining patients had a mean age of 60.0 ± 14.9 years, 57% were male, and the majority of White (49%) or Asian (37%) ethnicity. Data were complete for all variables, with the exception of the pre-operative vein and artery diameters, which were not documented for 3 and 10 patients respectively.

Clinical patency was achieved in 71% ($N=70$) of cases. 16 patients did not start haemodialysis during follow up, therefore functional maturation was attained in 65% of patients (53/82). The relationships between clinical patency and a range of pre-operative factors are reported in Table 6.1. None of the factors relating to patient demographics or co-morbidities were found to be significantly associated with fistula patency. As expected, AVFs were found to be significantly more likely to be patent in patients with upper arm (Brachio-Basilic or Brachio-cephalic) AVFs ($p=0.004$) and those with larger pre-operative artery diameters ($p=0.020$). Adverse events following surgery included two wound infections and one incidence of arteriovenous access ischaemic steal (AVAIS).

The relationship between temperature measurements and fistula clinical patency is shown in Table 6.2. For the proximal temperature measurements, no significant association was detected between fistula clinical patency and change ($p=0.338$) in relative temperature, therefore no further analysis was carried out. A ROC analysis

found the change in relative distal temperature to be a good predictor of clinical patency, with an area under the ROC curve (AUROC) of 0.86.

	N	Patent		p-Value
		No	Yes	
Age (Years)	98	58.6 ± 15.0	60.6 ± 15.0	0.552
Sex				0.258
Female	42	9 (21%)	33 (79%)	
Male	56	19 (34%)	37 (66%)	
Ethnicity				0.952
White	48	13 (27%)	35 (73%)	
Asian	36	11 (31%)	25 (69%)	
Black/Other	14	4 (29%)	10 (71%)	
Dialysis				1.000
No	64	18 (28%)	46 (72%)	
Yes	34	10 (29%)	24 (71%)	
Diabetes				0.819
No	60	18 (30%)	42 (70%)	
Yes	38	10 (26%)	28 (74%)	
Hypertension				1.000
No	14	4 (29%)	10 (71%)	
Yes	84	24 (29%)	60 (71%)	
AVF Side				0.803
Left	72	20 (28%)	52 (72%)	
Right	26	8 (31%)	18 (69%)	
AVF Type				0.004
BB	9	0 (0%)	9 (100%)	
BC	64	15 (23%)	49 (77%)	
RC	25	13 (52%)	12 (48%)	
Pre-op Vein Diameter (mm)	95	3.4 ± 0.9	3.7 ± 1.1	0.187
Pre-op Artery Diameter (mm)	88	3.6 ± 1.1	4.3 ± 1.3	0.020

Data reported as N (%), with p-values from Fisher's exact tests, or mean±SD, with p-values from t-tests, as applicable. Bold p-values are significant at p<0.05

Table 6.1 – Associations between patient factors and AVF clinical patency

	Patent*		p-Value	AUROC** (SE)
	No	Yes		
Relative Distal Temperature (°C)				
Change in temp.	+0.1 ± 0.9	-1.4 ± 1.2	<0.001	0.86 (0.05)
Relative Proximal Temperature (°C)				
Change in temp.	+0.1 ± 1.0	+0.2 ± 0.8	0.338	0.53 (0.07)

*Data reported as mean±SD, with p-values from t-tests

**Areas under ROC curves (with standard errors) for the predication of fistula maturation

Bold values are significant at p<0.05

Table 6.2 – Associations between distal and proximal relative temperatures and clinical patency

The analysis of relative temperatures found that a reduction in temperature from pre- to post-op was significantly associated with both clinical patency and functional maturation ($p<0.001$). The relationship between the change in relative distal temperature and clinical patency rate is reported in Figure 6.2, showing an increased rate of patency with a greater reduction in distal temperature. For the 22 patients whose relative distal temperature remained the same or increased post-operatively, only 3 (14%) achieved fistula clinical patency, compared to 88% of the 76 patients with a drop in relative temperature (Figure 6.2).

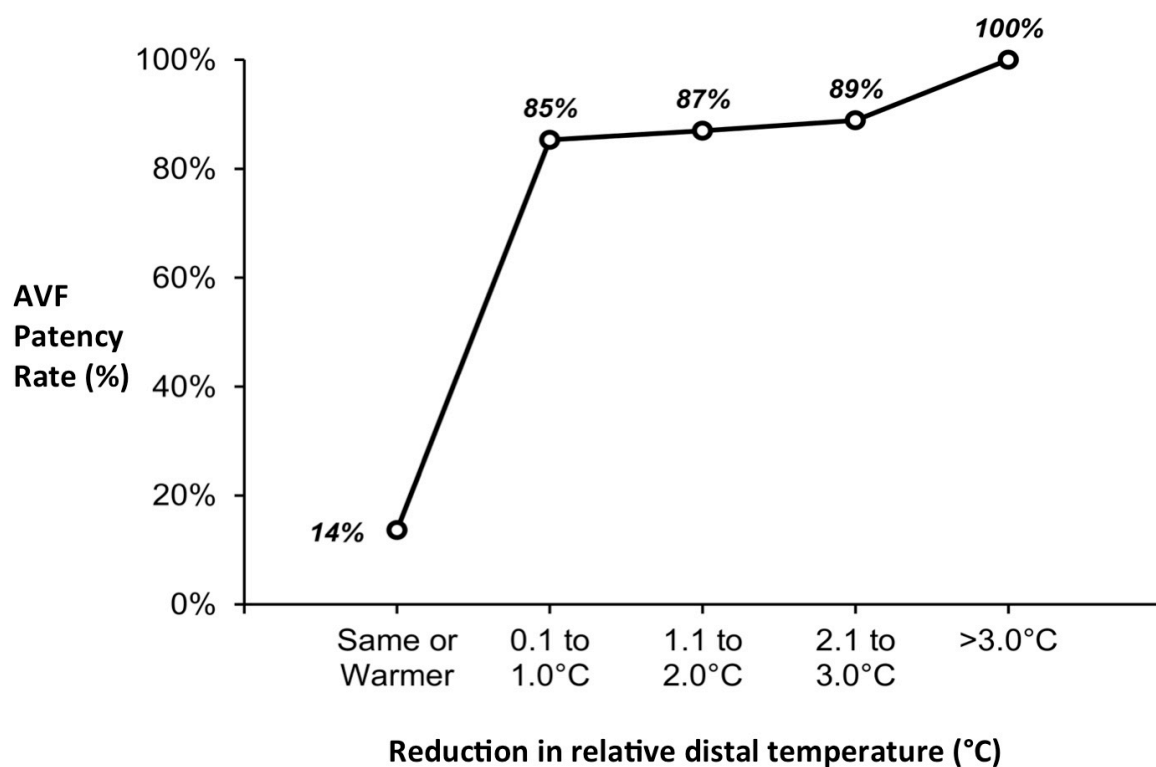


Figure 6.2 – Fistula patency rate by change in relative distal temperature

Analysis on two patient groups, based on the post-operative change in relative distal temperature was subsequently performed. Patients where the temperature remained the same or warmer, were compared to those where there was a decrease in relative temperature. A range of performance measures was calculated, to assess how

accurately this factor could predict both clinical patency and functional maturation (Table 6.3 and 6.4). For clinical patency, the factor was found to have a positive predictive value of 88%, a negative predictive value of 86%, a sensitivity of 96%, and specificity of 68%. For functional maturation, the factor was found to have a positive predictive value of 84%, a negative predictive value of 95%, a sensitivity of 98%, and specificity of 69%. Predictive accuracy was also assessed for the commonly used intra-operative predictor of thrill and was found to be much inferior than IRTI. In the sub-analysis, IRTI was found to be a good predictor of clinical patency for both upper arm and forearm fistulas (Table 6.5).

	Patent			Sensitivity	Specificity	PPV	NPV
	No	Yes	Rate				
Relative Change in Distal Temperature							
Colder Hand	9	67	88%	96%	68%	88%	86%
Same or Warmer	19	3	14%				
Thrill							
Yes	19	65	77%	93%	32%	77%	64%
No	9	5	36%				

Table 6.3 –Performance measures for predictors of clinical patency

	Matured			Sensitivity	Specificity	PPV	NPV
	No	Yes	Rate				
Relative Change in Distal Temperature							
Colder Hand	9	51	85%	96%	69%	85%	91%
Same or Warmer	20	2	9%				
Thrill							
Yes	20	50	71%	94%	31%	71%	75%
No	9	3	25%				

Table 6.4 –Performance measures for predictors of functional fistula maturation

	Patent		Rate	Sensitivity	Specificity	PPV	NPV
	No	Yes					
Relative Change in Distal Temperature Upper arm AVF							
Colder Hand	5	56	92%	97%	66%	92%	83%
Same or Warmer	10	2	17%				
Relative Change in Distal Temperature Forearm AVF							
Colder Hand	4	11	73%	92%	69%	73%	90%
Same or Warmer	9	1	10%				

Table 6.5 –Performance measures for IRTI depending on fistula type for clinical patency

A binary logistic regression model was then produced, in an attempt to identify the most predictive combination of these factors. The resulting model (Table 6.6) identified a reduced relative distal temperature as the best predictor of fistula maturation (odds ratio = 55.6, $p < 0.001$), but also identified pre-operative artery diameter > 4.3 as a second independent predictor (odds ratio = 6.8, $p = 0.021$). Vein diameter was not shown to be a significant independent predictor and this is likely due to exclusion of veins with a diameter of less than 2mm.

Factor	B*	Odds Ratio (95% CI)	p-Value
Colder Hand	4.0	55.6 (10.2 - 304.7)	<0.001
Pre-op Artery Diameter > 4.3 mm	1.9	6.8 (1.3 - 34.1)	0.021

Results are from a binary logistic regression model using a forwards stepwise entry procedure, and considering all of the factors in Table 3 for inclusion.

Analysis was based on the N=88 for whom pre-op artery diameters were available.

**Beta coefficient (i.e. log-odds)*

Bold p-values are significant at $p < 0.05$

Table 6.6 – Binary logistic regression model for the prediction of maturation

Dividing the coefficients from the resulting model by two, and rounding to the nearest integer meant that a simple risk score could be produced (Table 6.7). This score had a marginally improved AUROC over using the relative distal temperature change in isolation (0.89 vs. 0.86), with 100% of the 31 patients with the highest score achieving fistula maturation compared to 15% of the 15 patients with the lowest score. However, due to the relatively small sample size, this score would need to be validated on an external cohort before it can be recommended for use in practice.

Pre-op Artery Diameter > 4.3mm?	Colder Hand?	Score	N	Matured
No	No	0	13	2 (15%)
Yes	No	1	7	1 (14%)
No	Yes	2	37	28 (76%)
Yes	Yes	3	31	31 (100%)

AUROC=0.89 (SE=0.04)

Analysis was based on the N=88 for whom pre-op artery diameters were available.

Table 6.7 – Risk Score for maturation

6.5 DISCUSSION

Our findings demonstrate that infrared thermal imaging has a very good predictive ability, for both clinical patency and functional maturation. It has shown superiority to the commonly used intra-operative predictor of thrill. Comparing our results to the published literature on intra-operative flow measurement, IRTI has a better predictive value (Table 6.8).

Study	Predictor	Type of AVF	Number of patients	Sensitivity	Specificity	PPV	NPV
Our Study	IRT	Forearm	98	92%	69%	73%	90%
		Upper		97%	66%	92%	83%
		arm					
Berman	Intra- operative blood flow	Forearm	70	89%	62%	ns	ns
		Upper		79%	67%		
		arm					
Saucy	Intra- operative blood flow	Forearm	58	67%	75%	91%	38%

Table 6.8 – Comparison of predictive accuracy of intra-operative blood flow and infrared thermal imaging

Our study can have a direct impact on clinical practice. The ability to accurately predict AVF outcome means that patient post operative follow-up can be individually personalised and patient whose AVF is predicted to fail can be monitored more

closely. Possible causes of early AVF failure include surgical technique leading to a poor inflow and poor vein quality including stenotic lesions. So if an AVF is predicted to fail, a fistulogram could be organized with potentially a subsequent interventional procedure to treat any lesion and improve blood flow.

Previous studies have suggested that it takes as long as 10 weeks for an AVF to mature (Wilmink et al, 2016). The ability to accurately predict a failure would spare patients this long wait. In turn, this might reduce the length of dialysis catheter use, which is associated with both morbidity and mortality. For pre-dialysis patients, it would potentially increase the chances for them to start dialysis on a fistula. This is especially important as we know that there is a poor AVF conversion rate when a patient starts haemodialysis on a catheter.

In our cohort, there was only one incidence of haemodialysis access induced distal ischaemia (HAIDI). Interestingly, we found that ten patients had a larger drop in distal temperature than the patient who had HAIDI and none of them developed any symptoms. This would confirm that the key factor in the development of HAIDI is the inability of the arterial system to remodel and compensate for the diversion of blood flow (Inston et al, 2017).

In addition, our study also confirmed that upper arm fistulas matured significantly more than forearm fistulas. It has previously been reported that forearm fistulas have a higher risk of primary failure and failure to mature than upper arm AVFs (Peterson, Barker and Allon, 2008). We also found that a higher arterial diameter was significantly correlated with improved fistula maturation rate. This finding is confirmed by previous papers showing that pre-operative arterial diameters of radiocephalic AVF has been found to be associated inversely with immediate postoperative thrombosis and thrombosis up to 1 week after surgery (Wong et al, 1996).

In conclusion, infrared thermal imaging has been found to be an accurate and clinically useful post-operative tool in predicting AVF outcome. This can, at least, prompt close monitoring and clearly allow for early intervention to improve maturation rates.

Chapter 7

Discussion and conclusions

7.1 DISCUSSION

Every arteriovenous fistula has the potential to be the only vascular access a patient with end stage renal failure will ever need. It has a lower infection rate compared to both arteriovenous graft and tunnelled dialysis catheters. It has also been shown to require less interventions to keep it patent than grafts (Bittl J.A., 2010). Unfortunately for patients, this potential is not fulfilled often and therefore most patients will undergo multiple vascular access procedures during their dialysis lifetime. One of the biggest hurdles to achieve a patent long-term arteriovenous fistula is actually the first one with the maturation process. Failure to mature has been reported to be as high as 50% in some North American papers (Al-Jaishi et al, 2014) but it has traditionally been lower in Europe with rates of around 25% (Field M et al, 2016). Therefore it has been the most highly researched topic in vascular access.

Unfortunately to date, no adjuvant medical treatment has been able to improve this. A systematic review on this topic showed that the quality of the evidence was low due to short follow-up periods, the small number of studies for each comparison, heterogeneity between trials and moderate methodological quality of the studies due to incomplete reporting (Tanner N.C. and Da Silva A.F., 2016). This is probably due to the pathogenesis of non-maturation being poorly understood and therefore no clear target for therapy development.

Therefore until such therapy is available, being able to predict arteriovenous fistula maturation is important for the patient pathway as it will allow closer monitoring to AVFs at risk of non-maturation. Both venous and arterial diameters have been shown to be independent factors of maturation. The literature and our study (chapter 2) have shown numerous contradictions and therefore few pre-operative or intra-

operative factors were found to be good independent predictors of maturation (Farber A. et al, 2016). Our systematic review on predictive models found a small number of predictive models in vascular access. It concluded that the disparity between each study limits the development of a unified predictive model and more research is required in this field (chapter 3).

Infrared thermal imaging has been available for decades but recent development in technology has made it small, portable and easy to use. We have shown that this new available hardware is a valid, accurate and user-friendly mode of measuring skin temperature in humans and is comparable to more traditional methods of thermometry (Chapter 4). Another principal finding from our thesis is that infrared thermal imaging can be used to quantify reactive hyperaemia following a vascular occlusion test (Chapter 5). In addition IRTI can also show clearly those changes through the images taken at different time points. This is important when assessing the quality of new technology to be used clinically, especially in vascular surgery.

The IRTIVA study (Chapter 6) has also highlighted that a larger decrease in distal temperature post operatively correlates with an increased maturation rate. Therefore high flow into the vein at the time of surgery is the most important key factor for maturation and reduction in neointimal hyperplasia. This is consistent with the experience from French surgeons that regional anaesthesia offers improved rates of maturation as it results in vasodilation and increased blood flow compared to local anaesthesia. This was confirmed in a recently published randomised controlled trial showing significant improved rate of AVF patency when regional anaesthesia was used (84% vs 62%) (Aitken E. et al, 2016). A North American study investigated intraoperative blood flow measurements during AVF formation and found that matured fistulas had more than twice the blood flow at time of surgery than the ones

which did not mature (Berman SS et al, 2008). It has also recently been shown that AVF blood flow rate at day 1 is usually more than 50% of the 6-week blood flow rate (Robbin M.L. et al, 2016). Therefore a key component in future vascular research research should be to investigate local vasodilating agents, to increase blood flow into the vein at time of surgery, which last for the first 24 hours after surgery. For that purpose a recently published randomized controlled trial assessed the use of GTN transdermal patches in improving AVF outcome but unfortunately it did not show any improvement in maturation rate (Field M. et al, 2016). This could be due to the more systemic effect of the patches rather than one specifically targeting the fistula. Another agent PRT-201, a recombinant human type I pancreatic elastase, is currently being investigated to improve vascular access outcomes. In animal models, PRT-201 doses have been shown to fragment the majority of elastin in blood vessels resulting in a persistent vasodilation (Franano F.N. et al, 2007). The substance has been shown to be safe in humans and is awaiting robust results from larger studies (Hye R.J. et al, 2014).

7.2 CONCLUSIONS

Infrared thermal imaging can be used as noninvasive near patient test and it has been shown to be a valid user-friendly method of thermometry. The hypothesis that IRTI may be useful in prediction of VA outcomes has been explored in this thesis. It is clear that IRTI has a definite role in renal patients with vascular access as it was found to be an accurate and clinically useful post-operative tool in predicting AVF outcome. In addition, there is great potential for its use in other conditions such as peripheral vascular disease. It could be used as a non invasive near patient test in monitoring of outcomes following reperfusion interventions, both surgical and radiological ones. It might also be used as a predictor of outcome following renal transplantation. Therefore this thesis will be followed by research projects establishing the use of IRTI in both peripheral vascular disease and renal transplantation.

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APPENDIX

